AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	6/23/2017	for the District of Delaware

PLAINTIFF	DEFENDANT
BAYER INTELLECTUAL PROPERTY GMBH, BAYER AG, and JANSSEN PHARMACEUTICALS, INC.	INVAGEN PHARMACEUTICALS, INC.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	9,539,218	1/10/2017	Bayer Intellectual Property GmbH
2			
3			
4			
5			

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		
2		
3		
4		
5		

In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

Copy 1—Upon initiation of action, mail this copy to Director Copy 3—Upon termination of action, mail this copy to Director
Copy 2—Upon filing document adding patent(s), mail this copy to Director Copy 4—Case file copy

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	6/2/2017	for the District of Delaware

PLAINTIFF	DEFENDANT
BAYER INTELLECTUAL PROPERTY GMBH, BAYER AG, and JANSSEN PHARMACEUTICALS, INC.	ALEMBIC PHARMACEUTICALS LIMITED, ALEMBIC GLOBAL HOLDING SA, AND ALEMBIC PHARMACEUTICALS, INC.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	9,539,218	1/10/2017	Bayer Intellectual Property GmbH
2			
3			
4			
5			

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1			
2			
3			
4			
5			

In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

Copy 1—Upon initiation of action, mail this copy to Director **Copy 3—Upon termination of action, mail this copy to Director**
Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	5/26/2017	for the District of Delaware

PLAINTIFF	DEFENDANT
BAYER INTELLECTUAL PROPERTY GMBH, et al.	SIGMAPHARM LABORATORIES, LLC

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	9,539,218 B2	1/10/2017	Bayer Intellectual Property GmbH
2			
3			
4			
5			

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		
2		
3		
4		
5		

In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

Copy 1—Upon initiation of action, mail this copy to Director Copy 3—Upon termination of action, mail this copy to Director
Copy 2—Upon filing document adding patent(s), mail this copy to Director Copy 4—Case file copy

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	5/19/2017	for the District of Delaware

PLAINTIFF	DEFENDANT
BAYER INTELLECTUAL PROPERTY GMBH, et al.	MYLAN PHARMACEUTICALS INC.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	9,539,218 B2	1/10/2017	Bayer Intellectual Property GmbH
2			
3			
4			
5			

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		
2		
3		
4		
5		

In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

Copy 1—Upon initiation of action, mail this copy to Director Copy 3—Upon termination of action, mail this copy to Director
Copy 2—Upon filing document adding patent(s), mail this copy to Director Copy 4—Case file copy

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	5/12/2017	for the District of Delaware

PLAINTIFF	DEFENDANT
BAYER INTELLECTUAL PROPERTY GMBH, et al.	MICRO LABS LTD., MICRO LABS USA INC.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	9,539,218 B2	1/10/2017	Bayer Intellectual Property GmbH
2			
3			
4			
5			

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1			
2			
3			
4			
5			

In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

Copy 1—Upon initiation of action, mail this copy to Director Copy 3—Upon termination of action, mail this copy to Director
Copy 2—Upon filing document adding patent(s), mail this copy to Director Copy 4—Case file copy

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	4/28/2017	for the District of Delaware

PLAINTIFF	DEFENDANT
BAYER INTELLECTUAL PROPERTY GMBH, et al.	AUROBINDO PHARMA LIMITED, et al.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	9,539,218 B2	1/10/2017	Bayer Intellectual Property GmbH
2			
3			
4			
5			

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		
2		
3		
4		
5		

In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

Copy 1—Upon initiation of action, mail this copy to Director Copy 3—Upon termination of action, mail this copy to Director
Copy 2—Upon filing document adding patent(s), mail this copy to Director Copy 4—Case file copy

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	4/21/2017	for the District of Delaware

PLAINTIFF	DEFENDANT
BAYER INTELLECTUAL PROPERTY GMBH, et al.	TARO PHARMACEUTICAL INDUSTRIES LTD., et al.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	9,539,218 B2	1/10/2017	Bayer Intellectual Property GmbH
2			
3			
4			
5			

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		
2		
3		
4		
5		

In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

Copy 1—Upon initiation of action, mail this copy to Director Copy 3—Upon termination of action, mail this copy to Director
Copy 2—Upon filing document adding patent(s), mail this copy to Director Copy 4—Case file copy

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/883,218	01/10/2017	9539218	11987-00042	9960

21839 7590 12/21/2016

BUCHANAN, INGERSOLL & ROONEY PC
POST OFFICE BOX 1404
ALEXANDRIA, VA 22313-1404

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 2951 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Frank Misselwitz, Heidelberg, GERMANY;
Dagmar Kubitza, Ratingen, GERMANY;
Son-Mi Park, Wuppertal, GERMANY;
Klaus Wehling, Wuppertal, GERMANY;

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/883,218	07/16/2008	Frank Misselwitz	11987-00042	9960

7590 12/01/2016

BUCHANAN, INGERSOLL & ROONEY PC
POST OFFICE BOX 1404
ALEXANDRIA, VA 22313-1404

EXAMINER	
KAROL, JODY LYNN	

ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
12/01/2016	ELECTRONIC

NOTICE OF NON-COMPLIANT INFORMATION DISCLOSURE STATEMENT

An Information Disclosure Statement (IDS) filed 11.21.16 (both) in the above-identified application fails to meet the requirements of 37 CFR 1.97(d) for the reason(s) specified below. Accordingly, the IDS will be placed in the file, but the information referred to therein has not been considered.

The IDS is not compliant with 37 CFR 1.97(d) because:

☑ The IDS lacks a statement as specified in 37 CFR 1.97(e).

☐ The IDS lacks the fee set forth in 37 CFR 1.17(p).

☐ The IDS was filed after the issue fee was paid. Applicant may wish to consider filing a petition to withdraw the application from issue under 37 CFR 1.313(c) to have the IDS considered. See MPEP 1308.

NHB
for 571-272-4200 or 1-888-786-0101
Application Assistance Unit
Office of Data Management

FORM PTOM327-B (Rev. 02/08)

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any changes of address)

21839 1556 08/29/2016
BUCHANAN, INGERSOLL & ROONEY PC
POST OFFICE BOX 1404
ALEXANDRIA, VA 22313-1404

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/883,218	07/16/2008	Frank Misselwitz	11987-00042	9960

TITLE OF INVENTION: Prevention and Treatment of Thromboembolic Disorders

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEES DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	11/29/2016

EXAMINER	ART UNIT	CLASS-SUBCLASS
KAROL, JODY LYNN	1627	514-183000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Buchanan Ingersoll & Rooney PC
2
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: BAYER INTELLECTUAL PROPERTY GMBH

(B) RESIDENCE: (CITY and STATE OR COUNTRY) MONHEIM AM RHEIN, GERMANY

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:
- ☒ Issue Fee
- ☐ Publication Fee (No small entity discount permitted)
- ☐ Advance Order - # of Copies

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ☐ A check is enclosed.
- ☒ Payment by credit card. XXXXXXXXXXXX8868
- ☒ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number 024800 (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ☐ Applicant certifying micro entity status. See 37 CFR 1.29
- ☐ Applicant asserting small entity status. See 37 CFR 1.27
- ☐ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature: Christine M. Hansen Date: November 29, 2016

Typed or printed name: Christine M. Hansen Registration No. 40634

PTOL-85 Part B (10-13) Approved for use through 10/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Electronic Patent Application Fee Transmittal

Application Number:	11883218
Filing Date:	16-Jul-2008
Title of Invention:	Prevention and Treatment of Thromboembolic Disorders
First Named Inventor/Applicant Name:	Frank Misselwitz
Filer:	Christine Hansen/Darcy White
Attorney Docket Number:	11987-00042

Filed as Large Entity

Filing Fees for U.S. National Stage under 35 USC 371

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
UTILITY APPL ISSUE FEE	1501	1	960	960

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**960**

Electronic Acknowledgement Receipt

EFS ID:	27632672
Application Number:	11883218
International Application Number:	
Confirmation Number:	9960
Title of Invention:	Prevention and Treatment of Thromboembolic Disorders
First Named Inventor/Applicant Name:	Frank Misselwitz
Customer Number:	21839
Filer:	Christine Hansen/Darcy White
Filer Authorized By:	Christine Hansen
Attorney Docket Number:	11987-00042
Receipt Date:	29-NOV-2016
Filing Date:	16-JUL-2008
Time Stamp:	11:30:53
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$960
RAM confirmation Number	112916INTEFSW11322400
Deposit Account	024800
Authorized User	Christine Hansen

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

37 CFR 1.17 (Patent application and reexamination processing fees)

37 CFR 1.19 (Document supply fees)

37 CFR 1.20 (Post Issuance fees)

37 CFR 1.21 (Miscellaneous fees and charges)

37 CFR 1.492 (National application filing, search, and examination fees)

37 CFR 1.492(a) (Basic national fee only)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	IF_Trans_executed.pdf	436677 40ea842957f76095885bf0a263a9029fcc73a9d4	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30794 9002cc844b541cedfdb04ec882f094b1a1898346	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	467471		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Frank Misselwitz et al.

Application No.: 11/883,218 Confirmation No.: 9960

Filed: July 16, 2008 Art Unit: 1627

For: PREVENTION AND TREATMENT OF THROMBOEMBOLIC DISORDERS Examiner: Karol, Jody Lynn

INFORMATION DISCLOSURE STATEMENT (IDS) AND CERTIFICATION STATEMENT PURSUANT TO 37 C.F.R. §1.97(E)(1)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

Pursuant to 37 C.F.R. §§1.56, 1.97 and 1.98, the attention of the Patent and Trademark Office is hereby directed to the references submitted herewith. It is respectfully requested that the information be expressly considered during the prosecution of this application, and that the references be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

Consideration of this Information Disclosure Statement is believed appropriate pursuant 37 C.F.R. §1.97 (d). The Information Disclosure Statement is filed on or before payment of the issue fee and is accompanied by the fee set forth in 37 C.F.R. §1.17 (p). Furthermore, consideration of the references is believed proper under 37 C.F.R. §1.97 (e) because the references are the Patentee's Response to the Notices of Oppositions concerning European Patent 1 845 961with supporting documentation filed by Bayer Intellectual Property GmbH on November 16, 2016 in the European Patent Office. This Response was not filed until November 16, 2016 and therefore was not cited in a foreign patent office proceeding in a counterpart

foreign application more than three months prior to the filing of the Information Disclosure Statement.

Certain documents are in the German language: (1) Krauspe, R. "Der erste orale Faktor-Xa-Inhibitor Rivaroxaban (Xarelto®) zur Thromboseprophylaxe - eine neue Dimension." PZ Innovationspreis 2009, September 26, 2009, Düsseldorf, Germany; (2) "Thrombosen verhindern - eine Tablette kann Leben retten: Kurzbeschreibung der Institute und Unternehmen zu ihren nominierten Projekten Nominierte 2009," Deutscher Zukunftspreis, 2009; (3) "Xarelto®: Eine neue Dimension der Thromboseprophylaxe," version DE/2, Bayer Schering Pharma AG, May 2009; and (4) "Deutscher Zukunftspreis 2009 für Frank Misselwitz, Dagmar Kubitza und Elisabeth Perzborn," Pressemitteilung des Bundespräsidialamtes, December 2, 2009. A brief statement of their relevancy can be found in the discussion on pages 14-15 of the Patentee's Response to the Notices of Oppositions.

The reference Fülgraff, G and Palm D, Pharmakotherapie: Klinische Pharmakologie,11th ed., Urban & Fischer Verlag München, 2001, pp. 114-123, is in the German Language. A brief statement of its relevancy can be found on pages 52 and 71-72 of the Patentee's Response to the Notices of Oppositions. The reference Schmutzler, R and Novotny, U., Antikoagulation in Klinik und Praxis, ComMed Basel, Verlagsagentur, 1999, Chapter 4, pp. 76-93, is in the German language. A brief statement of its relevancy may be found on pages 59 and 95 of the Patentee's Response to the Notices of Oppositions. The reference Jaehde et al., Lehrbuch der Klinischen Pharmazie, 2nd ed., Wissenschaftliche Verlagsgesellschaft mbH Stuttgart, 2003, Chapter 9, pp. 129-139 is in the German language. A brief statement of its relevancy may be found on pages 68, 69, 102, 129, 135 and 136 of the Patentee's Response to the Notices of Oppositions. The reference Pschyrembel Klinisches Wörterbuch, 258th ed., Walter de Grunyter & Co., 1997, p. 714 is in the German language. A brief statement of its relevancy may be found on page 71 of the Patentee's Response to the Notices of Oppositions. The reference Aktories et al., Allgemeine und spezielle Pharmakologie und Toxikologie, 9th ed., Elsevier GmbH, München, 2005, pp. 72-74, is in the German language. A brief statement of its relevancy may be found on page 100 of the Patentee's Response to the Notices of Oppositions. The reference Aktories et al., Allgemeine

und spezielle Pharmakologie und Toxikologie, 9th ed., Elsevier GmbH, München, 2005, pp. 82-84 is in the German language. A brief statement of its relevancy may be found on pages 100 and 125 of the Patentee's Response to the Notices of Oppositions. The reference Mutschler, E et al., Mutschler Arzneimittelwirkungen, 8th ed., Wissenschaftliche Verlagsgesellschaft mbH Stuttgart, 2001, pp. 48-51 is in the German language. A brief statement of its relevancy may be found on pages 101, 102 and 134 of the Patentee's Response to the Notices of Oppositions. The reference Mutschler, E et al., Mutschler Arzneimittelwirkungen, 8th ed., Wissenschaftliche Verlagsgesellschaft mbH Stuttgart, 2001, p. 497 is in the German language. A brief statement of its relevancy may be found on page 147 of the Patentee's Response to the Notices of Oppositions. The reference Schwarz, JA, Leitfaden Klinische Prüfungen von Arzneimitteln und Medizinprodukten, 3rd ed., Editio Cantor Verlag für Medizin und Naturwissenschaften GmbH, Aulendorf, 2005, pp. 63-65 is in the German language. A brief statement of its relevancy may be found on page 107 of the Patentee's Response to the Notices of Oppositions. The reference Meier, J et al., Biopharmazie: Theorie und Praxis der Pharmakokinetik, Georg Thieme Verlag Stuttgart, 1981, Chapter 11.2.2, pp. 322-325 is in the German language. A brief statement of its relevancy may be found on page 126 of the Patentee's Response to the Notices of Oppositions. The reference Stapff, M. Arzneimittelstudien, 2nd ed., W. Zuckschwerdt Verlag GmbH, 2001, Chapter C5, pp. 48-49 is in the German language. A brief statement of its relevancy may be found on page 136 of the Patentee's Response to the Notices of Oppositions.

Previously, Applicants submitted copies of the grounds for Opposition and the references cited (that had not previously been cited) in these thirteen Oppositions. The Office considered these references. The application is now allowed.

In accordance with 37 CFR 1.98(a)(2)(ii), Applicant has not submitted copies of U.S. patents and U.S. patent applications. Applicant submits herewith copies of foreign patents and non-patent literature in accordance with 37 CFR 1.98(a)(2).

The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be

filed or which should have been filed for consideration of this paper herewith to our Deposit Account No. 02-4800, under Order No. 0081565-000006.

Dated: November 21, 2016

Respectfully submitted,

Electronic signature: /Christine M. Hansen/
Christine M. Hansen
Registration No.: 40,634
BUCHANAN INGERSOLL AND ROONEY PC
919 Market Street, Suite 1500
Wilmington, Delaware 19801-3046
(302) 552-4240
(302) 552-4295 (Fax)
Attorney for Applicant

Electronic Acknowledgement Receipt

EFS ID:	27582355
Application Number:	11883218
International Application Number:	
Confirmation Number:	9960
Title of Invention:	Prevention and Treatment of Thromboembolic Disorders
First Named Inventor/Applicant Name:	Frank Misselwitz
Customer Number:	21839
Filer:	Christine Hansen/Mich Sok
Filer Authorized By:	Christine Hansen
Attorney Docket Number:	11987-00042
Receipt Date:	22-NOV-2016
Filing Date:	16-JUL-2008
Time Stamp:	10:05:51
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	IDS_TL.pdf	236142 4473fb8753ddc0031984538 8f3f291f203d886f7	no	4

Warnings:

Information:	
Total Files Size (in bytes):	236142

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	11883218
Filing Date	2008-07-16
First Named Inventor	Frank MISSELWITZ et al.
Art Unit	1627
Examiner Name	KAROL, JODY LYNN
Attorney Docket Number	0081565-000006

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Patent citation information please click the Add button. Add

U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	11883218
	Filing Date	2008-07-16
	First Named Inventor	Frank MISSELWITZ et al.
	Art Unit	1627
	Examiner Name	KAROL, JODY LYNN
	Attorney Docket Number	0081565-000006

	1	Goodman and Gilman's THE PHARMACOLOGICAL BASIS OF THERAPEUTICS . 7th ed., Macmillan Publishing Company,1985, Chapter 1, pp. 3-34.	
	2	Goodman and Gilman's THE PHARMACOLOGICAL BASIS OF THERAPEUTICS . 10th ed., The McGraw-Hill Companies, Inc., 2001, Appendix II, pp. 1917-1924.	
	3	Goodman and Gilman's THE PHARMACOLOGICAL BASIS OF THERAPEUTICS . 10th ed., The McGraw-Hill Companies, Inc., 2001, 10th ed. 2001, Chapter 55, pp. 1519-1531.	
	4	Goodman and Gilman's THE PHARMACOLOGICAL BASIS OF THERAPEUTICS . 10th ed., The McGraw-Hill Companies, Inc., 2001, Chapter 3, pp. 48-56.	
	5	Goodman and Gilman's THE PHARMACOLOGICAL BASIS OF THERAPEUTICS . 7th ed., Macmillan Publishing Company, 1985, Chapter 58, pp. 1338-1352.	
	6	Birkett, DJ. "Pharmacokinetics made easy. The McGraw-Hill Companies, Inc., 2002, pp.20-23	
	7	Bayer Annual Report 2015 , 2015, p. 70 and p. 156.	
	8	'Fast Facts – About XARELTO® (rivaroxaban)." Janssen Pharmaceuticals, Inc., November 2011.	
	9	Summary of Product Characteristics for "Xarelto 10 mg film-coated tablets." European Medicines Agency, last updated July 1, 2015.	
	10	Summary of Product Characteristics for "Xarelto 20 mg film-coated tablets." European Medicines Agency, last updated May 20, 2016.	
	11	"Highlights of Prescribing Information" and "Full Prescribing Information" for XARELTO® (rivaroxaban)." Janssen Pharmaceuticals, Inc., revised May 2016.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	11883218
	Filing Date	2008-07-16
	First Named Inventor	Frank MISSELWITZ et al.
	Art Unit	1627
	Examiner Name	KAROL, JODY LYNN
	Attorney Docket Number	0081565-000006

	12	Krauspe, R. "Der erste orale Faktor-Xa-Inhibitor Rivaroxaban (Xarelto®) zur Thromboseprophylaxe - eine neue Dimension." PZ Innovationspreis 2009, September 26, 2009, Düsseldorf, Germany.	
	13	"Thrombosen verhindern - eine Tablette kann Leben retten: Kurzbeschreibung der Institute und Unternehmen zu ihren nominierten Projekten Nominierte 2009." Deutscher Zukunftspreis, 2009.	
	14	"Xarelto®: Eine neue Dimension der Thromboseprophylaxe." version DE/2, Bayer Schering Pharma AG, May 2009.	
	15	"Bayer's Xarelto® Recognised with 2010 International Prix Galien Award.", Bayer, October 7, 2010.	
	16	Bayer Annual Report 2009 , 2009, p. 38.	
	17	"Deutscher Zukunftspreis 2009 für Frank Misselwitz, Dagmar Kubitza und Elisabeth Perzborn." Pressemitteilung des Bundespräsidialamtes, December 2, 2009.	
	18	European Patent Office. "Communication pursuant to Article 94(3) EPC." EP Appl. No. 06 706 291.9; July 26, 2010.	
	19	Overview Table showing Opponents statements re half life being inherent property, Exh. D57 to Patentee's Response to Oppositions concerning European Patent 1 845 961, filed in EPO on November 16, 2016.	
	20	Overview Table showing Opponents statements re rapid-release tablet is common and therefore well-defined. Exh. D58 to Patentee's Response to Oppositions concerning European Patent 1 845 961, filed in EPO on November 16, 2016.	
	21	"CHMP Assessment Report for Xarelto." European Medicines Agency, Evaluation of Medicines for Human Use, Doc. Ref.: EMEA/543519/2008, 2008.	
	22	Search Results from Thomson Innovation regarding PCT-application recited in para [0031] of Opposed Patent, attached as Exh. D61 to Patentee's Response to Oppositions concerning European Patent 1 845 961, filed in EPO on November 16, 2016.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	11883218
	Filing Date	2008-07-16
	First Named Inventor	Frank MISSELWITZ et al.
	Art Unit	1627
	Examiner Name	KAROL, JODY LYNN
	Attorney Docket Number	0081565-000006

	23	Fülgraff, G and Palm D. Pharmakotherapie: Klinische Pharmakologie . 11th ed., Urban & Fischer Verlag München, 2001, pp. 114-123.	
	24	Schmutzler, R and Novotny, U. Antikoagulation in Klinik und Praxis . ComMed Basel, Verlagsagentur, 1999, Chapter 4, pp. 76-93.	
	25	Dugina, TN et al. "Receptors of the PAR family as a link between blood coagulation and inflammation." Biochemistry , vol. 67, no. 1, 2002, pp. 65-74.	
	26	"Points to consider on clinical investigation of medicinal products for prophylaxis of intra- and post-operative venous thromboembolic risk." The European Agency for the Evaluation of Medicinal Products, Committee For Proprietary Medicinal Products, CPMP/EWP/707/98, London, June 29, 2000.	
	27	European Patent Office. "Annex to Communication under Rule 71(3) EPC." EP Patent App. No. 06 706 291.9, November 13, 2014.	
	28	Jaehde et al. Lehrbuch der Klinischen Pharmazie . 2nd ed., Wissenschaftliche Verlagsgesellschaft mbH Stuttgart, 2003, Chapter 9, pp. 129-139.	
	29	Pschyrembel Klinisches Wörterbuch . 258th ed., Walter de Grunyter & Co., 1997, p. 714.	
	30	"Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L 311, 28.11.2001, p. 67)." November 28, 2012.	
	31	"EU Clinical Trials Register goes live." European Medicines Agency - Science, medicines, health, March 22, 2011.	
	32	Raffaella, C and Novak, A. "Publication of Study 'EurdraCT Number 2004-002171-16/Sweden'." European Medicines Agency Service Desk, posted May 24, 2016.	
	33	Patel, MR et al. "Rivaroxaban versus warfarin in nonvalvular atrial fibrillation." N Engl J Med , vol. 365, no. 10, 2011, pp. 883-891.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	11883218
	Filing Date	2008-07-16
	First Named Inventor	Frank MISSELWITZ et al.
	Art Unit	1627
	Examiner Name	KAROL, JODY LYNN
	Attorney Docket Number	0081565-000006

	34	Bayer Annual Report 2011, 2011, pp. 110-111.
	35	The EINSTEIN Investigators. "Oral rivaroxaban for symptomatic venous thromboembolism." N Engl J Med , vol. 363, no. 26, 2010, pp. 2499-510.
	36	The EINSTEIN-PE Investigators. "Oral rivaroxaban for the treatment of symptomatic pulmonary embolism." N Engl J Med , vol. 366, no. 14, 2012, pp. 1287-1297.
	37	Prins, MH et al. "Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies." Thromb J , vol. 11, 2013, pp. 1-10.
	38	Linkins, LA and Weitz JI. "New Anticoagulant Therapy." Annu Rev Med , vol. 56, 2005, pp. 63-77.
	39	Aktories et al. Allgemeine und spezielle Pharmakologie und Toxikologie. 9th ed., Elsevier GmbH, München, 2005, pp. 72-74.
	40	Aktories et al. Allgemeine und spezielle Pharmakologie und Toxikologie. 9th ed., Elsevier GmbH, München, 2005, pp. 82-84.
	41	Hauptmann, J and Stürzebecher J. "State of the art article: Synthetic inhibitors of thrombin and factor Xa: From Bench to bedside." Thrombosis Research , vol. 93, 1999, pp. 203-241.
	42	Mutschler, E et al. Mutschler Arzneimittelwirkungen. 8th ed., Wissenschaftliche Verlagsgesellschaft mbH Stuttgart, 2001, pp. 48-51.
	43	Mutschler, E et al. Mutschler Arzneimittelwirkungen. 8th ed., Wissenschaftliche Verlagsgesellschaft mbH Stuttgart, 2001, p. 497.
	44	Schwarz, JA. Leitfaden Klinische Prüfungen von Arzneimitteln und Medizinprodukten. 3rd ed., Editio Cantor Verlag für Medizin und Naturwissenschaften GmbH, Aulendorf, 2005, pp. 63-65.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	11883218
	Filing Date	2008-07-16
	First Named Inventor	Frank MISSELWITZ et al.
	Art Unit	1627
	Examiner Name	KAROL, JODY LYNN
	Attorney Docket Number	0081565-000006

	45	Page, C et al. Integrated pharmacology. 2nd ed., Mosby International Ltd, 2002, pp. 210-211.
	46	Summary of Product Characteristics for "Eliquis 2.5 mg film-coated tablets." European Medicines Agency, last updated January 22, 2016.
	47	Meier, J et al. Biopharmazie: Theorie und Praxis der Pharmakokinetik . Georg Thieme Verlag Stuttgart, 1981, Chapter 11.2.2, pp. 322-325.
	48	Stapff, M. Arzneimittelstudien . 2nd ed., W. Zuckschwerdt Verlag GmbH, 2001, Chapter C5, pp. 48-49.
	49	Bisio, A et al. "Structural features of low-molecular-weight heparins affecting their affinity to antithrombin." Thromb Haemost, vol. 102, 2009, pp. 865-873.
	50	Harenberg, J et al. "Update of the recommendations on biosimilar low-molecular-weight heparins from the Scientific Subcommittee on Control of Anticoagulation of the International Society on Thrombosis and Haemostasis." Journal of Thrombosis and Haemostasis , vol. 11, no. 7, 2013, pp. 1421-1425.

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	11883218
Filing Date	2008-07-16
First Named Inventor	Frank MISSELWITZ et al.
Art Unit	1627
Examiner Name	KAROL, JODY LYNN
Attorney Docket Number	0081565-000006

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☒ See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Christine M. Hansen/	Date (YYYY-MM-DD)	2016-11-21
Name/Print	Christine M. Hansen	Registration Number	40,634

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	11883218
Filing Date	2008-07-16
First Named Inventor	Frank MISSELWITZ et al.
Art Unit	1627
Examiner Name	KAROL, JODY LYNN
Attorney Docket Number	0081565-000006

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Patent citation information please click the Add button. Add

U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	11883218
	Filing Date	2008-07-16
	First Named Inventor	Frank MISSELWITZ et al.
	Art Unit	1627
	Examiner Name	KAROL, JODY LYNN
	Attorney Docket Number	0081565-000006

	1	Patentee's Response to the Notices of Opposition concerning European Patent 1 845 961 (06 706 291.9) "Treatment of thromboembolic disorders with rivaroxaban," (submitted to EPO on November 16, 2016), Cohausz & Florack, pp. 1-168.

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	11883218
Filing Date	2008-07-16
First Named Inventor	Frank MISSELWITZ et al.
Art Unit	1627
Examiner Name	KAROL, JODY LYNN
Attorney Docket Number	0081565-000006

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☒ See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Christine M. Hansen/	Date (YYYY-MM-DD)	2016-11-21
Name/Print	Christine M. Hansen	Registration Number	40,634

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Patent Application Fee Transmittal

Application Number:	11883218
Filing Date:	16-Jul-2008
Title of Invention:	Prevention and Treatment of Thromboembolic Disorders
First Named Inventor/Applicant Name:	Frank Misselwitz
Filer:	Christine Hansen/Mich Sok
Attorney Docket Number:	11987-00042

Filed as Large Entity

Filing Fees for U.S. National Stage under 35 USC 371

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**180**

Electronic Acknowledgement Receipt

EFS ID:	27574572
Application Number:	11883218
International Application Number:	
Confirmation Number:	9960
Title of Invention:	Prevention and Treatment of Thromboembolic Disorders
First Named Inventor/Applicant Name:	Frank Misselwitz
Customer Number:	21839
Filer:	Christine Hansen/Mich Sok
Filer Authorized By:	Christine Hansen
Attorney Docket Number:	11987-00042
Receipt Date:	21-NOV-2016
Filing Date:	16-JUL-2008
Time Stamp:	15:51:12
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$180
RAM confirmation Number	112216INTEFSW15521901
Deposit Account	024800
Authorized User	Mich Sok

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

37 CFR 1.17 (Patent application and reexamination processing fees)

37 CFR 1.19 (Document supply fees)

37 CFR 1.20 (Post Issuance fees)

37 CFR 1.21 (Miscellaneous fees and charges)

37 CFR 1.492 (National application filing, search, and examination fees)

37 CFR 1.492(a) (Basic national fee only)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Information Disclosure Statement (IDS) Form (SB08)	PTO_SB08.pdf	615814 ac9a9784db2cd917750b2e7995deaecad6bb9d6c	no	8
Warnings:					
Information:					
A U.S. Patent Number Citation or a U.S. Publication Number Citation is required in the Information Disclosure Statement (IDS) form for autoloading of data into USPTO systems. You may remove the form to add the required data in order to correct the Informational Message if you are citing U.S. References. If you chose not to include U.S. References, the image of the form will be processed and be made available within the Image File Wrapper (IFW) system. However, no data will be extracted from this form. Any additional data such as Foreign Patent Documents or Non Patent Literature will be manually reviewed and keyed into USPTO systems.					
2	Information Disclosure Statement (IDS) Form (SB08)	PTO_SB08_II.pdf	612099 cdf9799793f928667b75fcecbab1a60bcdaf84d9	no	4
Warnings:					
Information:					
A U.S. Patent Number Citation or a U.S. Publication Number Citation is required in the Information Disclosure Statement (IDS) form for autoloading of data into USPTO systems. You may remove the form to add the required data in order to correct the Informational Message if you are citing U.S. References. If you chose not to include U.S. References, the image of the form will be processed and be made available within the Image File Wrapper (IFW) system. However, no data will be extracted from this form. Any additional data such as Foreign Patent Documents or Non Patent Literature will be manually reviewed and keyed into USPTO systems.					
3	Non Patent Literature	NPL1.pdf	9904714 a2838eb0cb6827f2a7570f945fa91aba0539ddd9	no	34
Warnings:					
Information:					
4	Non Patent Literature	NPL2.pdf	2783227 486223fdc65b1fbf04d364140f2214f5e4ecede3	no	10
Warnings:					
Information:					
5	Non Patent Literature	NPL3.pdf	4329845 244ffa55c1778edba9c02cef72a3dcf1e8f7515 4	no	15
Warnings:					

Information:					
6	Non Patent Literature	NPL4.pdf	3237222 fbcc160e666831b522ef43108088078d4f7748fa	no	11
Warnings:					
Information:					
7	Non Patent Literature	NPL5.pdf	4814890 ab46d9f671091b5f2139b207b50790e63ad6504b	no	17
Warnings:					
Information:					
8	Non Patent Literature	NPL6.pdf	885854 82db2151d444afc64c8374d080cc7da86d938b7a	no	4
Warnings:					
Information:					
9	Non Patent Literature	NPL7.pdf	158208 42be3288d7a2337f48f1620b46979236cd071dec	no	3
Warnings:					
Information:					
10	Non Patent Literature	NPL8.pdf	2593468 f43838c73384c73c8a8b350d25367629c6562060	no	4
Warnings:					
Information:					
11	Non Patent Literature	NPL9.pdf	2861548 c0883712804fafb097ceba6d18dc78efa42bc513	no	16
Warnings:					
Information:					
12	Non Patent Literature	NPL10.pdf	4430005 eb1f9600f74cc73334778838f69892a7c257e94a	no	23
Warnings:					
Information:					

13	Non Patent Literature	NPL11.pdf	1153883 a55c022cf041754ff3ef59259d7f736200a6cf4d	no	49
Warnings:					
Information:					
14	Non Patent Literature	NPL12.pdf	433265 d2569f429d7f52ac7c656a0fe31466b7aca93d60	no	3
Warnings:					
Information:					
15	Non Patent Literature	NPL13.pdf	484747 aa7ee243a23a0b33f29f5e2e9a1e5eafc12dde9f	no	3
Warnings:					
Information:					
16	Non Patent Literature	NPL14.pdf	1209949 1cb379b9aaa7afb813cf0ff5725875a7026536b5	no	7
Warnings:					
Information:					
17	Non Patent Literature	NPL15.pdf	200417 3fb1b5f3d558cd09256709bd56bd773f65e2841d	no	4
Warnings:					
Information:					
18	Non Patent Literature	NPL16.pdf	832770 a5d1413e39f0aa82ecd3d3d169b44de85ed9ad07	no	2
Warnings:					
Information:					
19	Non Patent Literature	NPL17.pdf	754749 0e169f20572c663aad5112065b0c041ecd45d35e	no	1
Warnings:					
Information:					

20	Non Patent Literature	NPL18.pdf	813947 161e467993fedccf24c3d32b493d234ac8282e89	no	6
Warnings:					
Information:					
21	Non Patent Literature	NPL19.pdf	93381 ce70392b4cb4c3251050f57d5063c75901ca8830	no	2
Warnings:					
Information:					
22	Non Patent Literature	NPL20.pdf	92642 587d49d6dc9a97e10b27a13ea701b5e4e17be946	no	2
Warnings:					
Information:					
23	Non Patent Literature	NPL21.pdf	1055026 c2be062802510a0862be04352e15cdfdc0fd9f4b	no	56
Warnings:					
Information:					
24	Non Patent Literature	NPL22.pdf	95196 2a606c06ff2722e180805a425d3f81eac47443ae	no	3
Warnings:					
Information:					
25	Non Patent Literature	NPL23.pdf	3200344 96bc81bf0b1db09ef154b5d15fab9767bcca0f82	no	12
Warnings:					
Information:					
26	Non Patent Literature	NPL24.pdf	2772642 3c7191f64ba8d40dbde760ffc92ed775ba419f91	no	12
Warnings:					
Information:					

27	Non Patent Literature	NPL25.pdf	137190 c2c043be332c8059d9a2b1f6939f27446afe28b5	no	10
Warnings:					
Information:					
28	Non Patent Literature	NPL26.pdf	430853 e21da5e44125508ba6911d35d35a50194dea7f50	no	6
Warnings:					
Information:					
29	Non Patent Literature	NPL27.pdf	459448 b61ffc9a4e2f1e718046b471ebc50e3cc15987a0	no	3
Warnings:					
Information:					
30	Non Patent Literature	NPL28.pdf	1741436 63f0757486139336e171aa9a678b16b9e1814514	no	13
Warnings:					
Information:					
31	Non Patent Literature	NPL29.pdf	513099 baf847e1ff173f773c5bd32b746aeaacbd1a6b0a	no	3
Warnings:					
Information:					
32	Non Patent Literature	NPL30.pdf	1017661 e35c3237af242adca3160e9cf81be6764f567b24	no	188
Warnings:					
Information:					
33	Non Patent Literature	NPL31.pdf	110975 068d805ee9dec885ef1c2e2f4619928307e6fd82	no	2
Warnings:					
Information:					

34	Non Patent Literature	NPL32.pdf	238605 924a78d041ae0b077ef2f762e1d3249303b736c2	no	5
Warnings:					
Information:					
35	Non Patent Literature	NPL33.pdf	225513 fc88730b51aa0c5ae877a6ff08bcc7fe8287b672	no	9
Warnings:					
Information:					
36	Non Patent Literature	NPL34.pdf	312204 54d6b41218ea68c112deeea89703c179ff252081	no	3
Warnings:					
Information:					
37	Non Patent Literature	NPL35.pdf	192954 95a89bf3ee4dc2f3c9b186e82836b49e576d32c1	no	12
Warnings:					
Information:					
38	Non Patent Literature	NPL36.pdf	193889 516aec696d9cafb9631714edbfce022045bb4ab7	no	11
Warnings:					
Information:					
39	Non Patent Literature	NPL37.pdf	190689 baaf0145ccc8e97ab3534a8fa2373986402b705a	no	10
Warnings:					
Information:					
40	Non Patent Literature	NPL38.pdf	175370 8102eb9ecf0631ea5ac0bfa6fa8afa8c6b6c2082	no	15
Warnings:					
Information:					

41	Non Patent Literature	NPL39.pdf	1150985 aa9c9cca10fc55cb955ee3494508d2e15d343bf5	no	5
Warnings:					
Information:					
42	Non Patent Literature	NPL40.pdf	2407587 282d1d62b17e4f61441718e8092214d9f18268da	no	5
Warnings:					
Information:					
43	Non Patent Literature	NPL41.pdf	476405 cb22799e6dfd40563906a25362db0b328a371d65	no	39
Warnings:					
Information:					
44	Non Patent Literature	NPL42.pdf	2228598 f0b8fa8cfd866ea34fc80483f149aa94b89a62e2	no	6
Warnings:					
Information:					
45	Non Patent Literature	NPL43.pdf	352749 1cc4938985a8f4bd906e6356b723f9941bfccf2d	no	3
Warnings:					
Information:					
46	Non Patent Literature	NPL44.pdf	1004444 411d0d9de27b6d52cbbcf1f63d40852a5f11c0cb	no	5
Warnings:					
Information:					
47	Non Patent Literature	NPL45.pdf	1705789 fb8cd4f851522424bd3529682072 0d7e96782577	no	4
Warnings:					
Information:					

48	Non Patent Literature	NPL46.pdf	2739434 bc2dd45aa041d2737770357f6027131e8a3cc2cf	no	46
Warnings:					
Information:					
49	Non Patent Literature	NPL47.pdf	963562 84e25b13e67b64d2a5a7c123bf4f03379942d03c	no	6
Warnings:					
Information:					
50	Non Patent Literature	NPL48.pdf	514963 9b60460971e8da98aa9632cbacac7ad783081101	no	3
Warnings:					
Information:					
51	Non Patent Literature	NPL49.pdf	2443043 c53244cacc3841d7043d262aa90bd5da12ecba2a	no	9
Warnings:					
Information:					
52	Non Patent Literature	NPL50.pdf	104960 dc6b2bcabd0284147bbbadb88978e2ecc2ae2c68	no	5
Warnings:					
Information:					
53	Non Patent Literature	NPL51.pdf	2224073 dd2a36b03368786fd3b90a81b1d0a604ca8639f2	no	168
Warnings:					
Information:					
54	Fee Worksheet (SB06)	fee-info.pdf	30295 68936793319ccc71a7b5db19ac09ff149dde76f9	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	74706625	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

21839 7590 08/29/2016
BUCHANAN, INGERSOLL & ROONEY PC
POST OFFICE BOX 1404
ALEXANDRIA, VA 22313-1404

EXAMINER
KAROL, JODY LYNN

ART UNIT	PAPER NUMBER
1627	

DATE MAILED: 08/29/2016

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/883,218	07/16/2008	Frank Misselwitz	11987-00042	9960

TITLE OF INVENTION: Prevention and Treatment of Thromboembolic Disorders

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	11/29/2016

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

21839 7590 08/29/2016
BUCHANAN, INGERSOLL & ROONEY PC
POST OFFICE BOX 1404
ALEXANDRIA, VA 22313-1404

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/883,218	07/16/2008	Frank Misselwitz	11987-00042	9960

TITLE OF INVENTION: Prevention and Treatment of Thromboembolic Disorders

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	11/29/2016

EXAMINER	ART UNIT	CLASS-SUBCLASS
KAROL, JODY LYNN	1627	514-183000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:
- ❑ Issue Fee
- ❑ Publication Fee (No small entity discount permitted)
- ❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ❑ A check is enclosed.
- ❑ Payment by credit card. Form PTO-2038 is attached.
- ❑ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ❑ Applicant certifying micro entity status. See 37 CFR 1.29 — NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
- ❑ Applicant asserting small entity status. See 37 CFR 1.27 — NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
- ❑ Applicant changing to regular undiscounted fee status. — NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/883,218	07/16/2008	Frank Misselwitz	11987-00042	9960

21839 7590 08/29/2016

BUCHANAN, INGERSOLL & ROONEY PC
POST OFFICE BOX 1404
ALEXANDRIA, VA 22313-1404

EXAMINER	
KAROL, JODY LYNN	

ART UNIT	PAPER NUMBER
1627	

DATE MAILED: 08/29/2016

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 11/883,218	Applicant(s) MISSELWITZ ET AL.	
	Examiner JODY KAROL	Art Unit 1627	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *6/3/2016*.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on_____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *1, 17, 18, and 19*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 8/5/2016
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☒ Interview Summary (PTO-413), Paper No./Mail Date *20160822* .
5. ☒ Examiner's Amendment/Comment
6. ☒ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

DETAILED ACTION

In view of the Patent Board Decision filed on 6/3/2016 affirming the Examiner in part, the finality of the previous Office action filed 9/21/2011 is herein withdrawn.

Claims 7-9, 11, 15, 1-17 and are 19 were previously withdrawn as pertaining to the non-elected invention. Claims 1, 4, 5, 7-9, 11, and 15-19 are pending.

Information Disclosure Statement

1. The information disclosure statement (IDS) filed on 8/5/2016 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered.

Election/Restrictions

2. Claim 1 as amended *infra* is allowable. The restriction requirement among species of thromboembolic disorders, as set forth in the Office action mailed on 11/10/2010, has been reconsidered in view of the allowability of claims to the elected invention pursuant to MPEP § 821.04(a). **The restriction requirement is hereby withdrawn as to any claim that requires all the limitations of an allowable claim.** Specifically, the restriction requirement of11/10/2010 is partially withdrawn. Claims 17 and 19, directed to pulmonary embolism and stroke are no longer withdrawn from consideration because the claim(s) requires all the limitations of an allowable claim. However, claims 7-9, 11, and 15, and 16 directed to pharmaceutical compositions and

thromboembolic disorders outside the scope of claim 1 are withdrawn from consideration because they do not require all the limitations of an allowable claim.

In view of the above noted withdrawal of the restriction requirement, applicant is advised that if any claim presented in a continuation or divisional application is anticipated by, or includes all the limitations of, a claim that is allowable in the present application, such claim may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application.

Once a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. See In re Ziegler, 443 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

WITHDRAWN REJECTIONS

3. In view of the Patent Board Decision filed on 6/3/2016 affirming the Examiner in part and the Examiner's amendment presented *infra*, the rejection of claims 1, 4, 5, 11, and 18 on the ground of nonstatutory double patenting over claims 13, 24, and 30 of commonly assigned U.S. Patent No. 7,157,456 B2 in view of Kubitza et al.[1] ("Multiple dose escalation study investigating the pharmacodynamics, safety, and pharmacokinetics of BAY 59-7939 an oral, direct Factor Xa inhibitor in healthy male subjects," *Blood,* Vol. 102:11 16 Nov. 2003, pgs 811a) and Kubitza et al.[2] (ABSTRACT 2010, "Single Dose escalation study investigating the pharmacodynamics, safety, and pharmacokinetics of BAY 59-7939 an oral, direct Factor Xa inhibitor in healthy male subjects," *Blood,* Vol. 102:11, 16 Nov. 2003, page 813a) is herein withdrawn.

4. In view of the Patent Board Decision filed on 6/3/2016 affirming the Examiner in part and the Examiner's amendment presented *infra*, the rejection of claims 1, 4, 5, 11, and 18 on the ground of nonstatutory double patenting over claims 1-6 and 17-21 over commonly assigned U.S. Patent No. 7,592,399 B2 in view of Kubitza et al.[1] ("Multiple dose escalation study investigating the pharmacodynamics, safety, and pharmacokinetics of BAY 59-7939 an oral, direct Factor Xa inhibitor in healthy male subjects," *Blood,* Vol. 102:11 16 Nov. 2003, pgs 811a) and Kubitza et al.[2] (ABSTRACT 2010, "Single Dose escalation study investigating the pharmacodynamics, safety, and pharmacokinetics of BAY 59-7939 an oral, direct Factor Xa inhibitor in healthy male subjects," *Blood,* Vol. 102:11, 16 Nov. 2003, page 813a) is herein withdrawn.

5. In view of the Patent Board Decision filed on 6/3/2016 affirming the Examiner in part and the Examiner's amendment presented *infra*, the rejection of claims 1, 4, 5, 11, and 18 under 35 U.S.C. 103(a) as being unpatentable over Straub et al. (US 2003/05310 A1) in view of Kubitza et al.[1] ("Multiple dose escalation study investigating the pharmacodynamics, safety, and pharmacokinetics of BAY 59-7939 an oral, direct Factor Xa inhibitor in healthy male subjects," *Blood,* Vol. 102:11 16 Nov. 2003, pgs 811a) and Kubitza et al.[2] (ABSTRACT 2010, "Single Dose escalation study investigating the pharmacodynamics, safety, and pharmacokinetics of BAY 59-7939 an oral, direct Factor Xa inhibitor in healthy male subjects," *Blood,* Vol. 102:11, 16 Nov. 2003, page 813a) is herein withdrawn.

6. In view of the amendment filed on 1/30/2012, the rejection of claims 1, 4, 5, 11, and 18 under U.S.C. 35 112, second paragraph, as being indefinite, was previously withdrawn in the Examiner's answer filed on 11/22/2013.

7. The rejection of claims 1, 4, 5, 11 and 18 as being directed to an invention not patentably distinct from claims 13, 24, and 30 of commonly assigned US 7,157,456 B2 was previously withdrawn in Examiner's answer filed on 11/22/2013.

8. The rejection of claims 1, 4, 5, 11 and 18 as being directed to an invention not patentably distinct from claims 1-6 and 17-21 of commonly assigned US 7,592,399 B2 was previously withdrawn in Examiner's answer filed on 11/22/2013.

EXAMINER'S AMENDMENT

9. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in an interview with Christine Hansen on 8/22/2016.

The application has been amended as follows:

Please cancel claims 4, 5, 7-9, 11, 15, and 16.

In claim 1, line 4, after “rapid release”; **delete** "oral dosage form" and **insert** --tablet--.

In claim 1, line 5, after “patient in need thereof”; **insert** --, wherein the thromboembolic disorder is selected from the group consisting of pulmonary embolisms, deep vein thromboses, and stroke--.

Reasons for Allowance

10. The following is an examiner’s statement of reasons for allowance: Claims 1 and 17-19 are directed to a method of treating a thromboembolic disorder comprising administering a direct factor Xa inhibitor that is 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide (i.e. rivoroxaban) no more than once daily for at least five consecutive days in a rapid-release oral dosage table to a patient in nee thereof, wherein the thromboembolic disorder selected from the group consisting of pulmonary embolisms, deep vein thromboses, and stroke.

The claims are allowable over the closest cited prior art, Straub et al. (US 2003/05310 A1) in view of Kubitza et al.[1] ("Multiple dose escalation study investigating the pharmacodynamics, safety, and pharmacokinetics of BAY 59-7939 an oral, direct Factor Xa inhibitor in healthy male subjects," *Blood,* Vol. 102:11 16 Nov. 2003, pgs 811a) and Kubitza et al.[2] (ABSTRACT 2010, "Single Dose escalation study investigating the pharmacodynamics, safety, and pharmacokinetics of BAY 59-7939 an oral, direct Factor Xa inhibitor in healthy male subjects," *Blood,* Vol. 102:11, 16 Nov. 2003, page

813a), because the cited prior art does not teach, disclose nor render obvious the instantly claimed method wherein a rapid-release tablet is utilized. In the Patent Board Decision filed on 6/3/2016, the Board states that the "rapid-release tablet" is interpreted in view of the express definition in the Specification which is "those [tablets] which, according to USP release apparatus 2 (paddle), have a Q value of (30 minutes) 75%." The Board further states that Kubitza et al.[2] cannot be considered to teach or render obvious a tablet that is a rapid release tablet because the only disclosure in Kubitza et al.[2] directed to drug release by tablets is that "[l]ower peak concentrations of approximately 50% were observed 2 hours after administration of the tablet." Thus, while Straub et al. in view of Kubitza et al.[1] and Kubitza[2] render obvious a method of treating the claimed thromboembolic disorders comprising administering rivoroxaban no more than only daily for at least five consecutive days in a rapid release oral dosage form, they do not teach or render obvious said methods wherein a rapid-release tablet is utilized.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled “Comments on Statement of Reasons for Allowance.”

Conclusion

Claims 1 and 17-19 are allowed.

Correspondence

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jody L. Karol whose telephone number is (571)270-3283. The examiner can normally be reached on 8:30 am - 5:00 pm Mon-Fri EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Jody L. Karol/

Examiner, Art Unit 1627

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1627

Examiner-Initiated Interview Summary	Application No.	Applicant(s)	
	11/883,218	MISSELWITZ ET AL.	
	Examiner	Art Unit	
	JODY KAROL	1627	

All participants (applicant, applicant's representative, PTO personnel):

(1) *JODY KAROL*. (3)_____.

(2) *Christine Hansen*. (4)_____.

Date of Interview: *22 August 2016*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☐ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☐103 ☐Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *1,4,5,7-9,11 and 15-19*.

Identification of prior art discussed: _____.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

Obtained approval for the modified Examiner's amendment inititially proposed on 8/18/2016. The modified Examiner's amendment is described in detail in the Allowability Notice.

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/JODY KAROL/ Examiner, Art Unit 1627	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	11883218
Filing Date	2008-07-16
First Named Inventor	Frank MISSELWITZ et al.
Art Unit	1627
Examiner Name	KAROL, JODY LYNN
Attorney Docket Number	0081565-000006

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Patent citation information please click the Add button. Add

U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

/Jody Karol/ 08/17/2016

Receipt date: 08/05/2016	Application Number	11883218 11883218 - GAU: 1627
INFORMATION DISCLOSURE STATEMENT BY APPLICANT **(Not for submission under 37 CFR 1.99)**	Filing Date	2008-07-16
	First Named Inventor	Frank MISSELWITZ et al.
	Art Unit	1627
	Examiner Name	KAROL, JODY LYNN
	Attorney Docket Number	0081565-000006

/J.K./	1	Substantiation of the Opposition, Application/Patent: 06706291.9/EP 1 845 961 B1, "Treatment of Thromboembolic Disorders With Rivaroxaban," (December 30, 2015), Henkel, Breuer & Partner, pp. 1-25.	
/J.K./	2	Statement of Opposition, Application/Patent: 06706291.9/EP 1 845 961 B1, "Treatment of Thromboembolic Disorders With Rivaroxaban," (January 6, 2016), Elkington and Fife LLP, Opponent: Actavis Group PTC ehf, pp. 1-12.	
/J.K./	3	Notice of Opposition to a European Patent, Application/Patent: 06706291.9/EP 1 845 961 B1, "Treatment of Thromboembolic Disorders With Rivaroxaban," (January 21, 2016), Opponent: Abdi Ibrahim Ilac Sanayi ve Ticaret A.S., pp. 1-9.	
/J.K./	4	Statement of Grounds for Opposition, Application/Patent: 06706291.9/EP 1 845 961 B1, "Treatment of Thromboembolic Disorders With Rivaroxaban," (January 21, 2016), Opponent: Generics Ltd.; Elend, Almut Susanne Authorised Representative, pp. 1-10.	
/J.K./	5	The Opposition patent, Application/Patent: 06706291.9/EP 1 845 961 B1, "Treatment of Thromboembolic Disorders With Rivaroxaban," (January 21, 2016), Opponent: Alexander Wittkopp, pp. 1-14.	
/J.K./	6	Opposition, Application/Patent: 06706291.9/EP 1 845 961 B1, "Treatment of Thromboembolic Disorders With Rivaroxaban," (January 21, 2016), Opponent: STADA Arzneimittel AG, and an English Translation, pp. 1-27.	
/J.K./	7	Opposition, Application/Patent: 06706291.9/EP 1 845 961 B1, "Treatment of Thromboembolic Disorders With Rivaroxaban," (January 21, 2016), Opponent: Teva Pharmaceutical Industries Ltd, pp. 1-14.	
/J.K./	8	Statement of Opposition, Application/Patent: 06706291.9/EP 1 845 961 B1, "Treatment of Thromboembolic Disorders With Rivaroxaban," (January 21, 2016), Opponent: Zaklady Farmaceutyczne Polpharma SA, pp.1-12.	
/J.K./	9	Opposition, Application/Patent: 06706291.9/EP 1 845 961 B1, "Treatment of Thromboembolic Disorders With Rivaroxaban," (January 22, 2016), Opponent: ABG Patentes, S.L., pp. 1-22.	
/J.K./	10	Opposition, Application/Patent: 06706291.9/EP 1 845 961 B1, "Treatment of Thromboembolic Disorders With Rivaroxaban," (January 22, 2016), Opponent: Galenicum Health S.L., pp. 1-19.	
/J.K./	11	Opposition, Application/Patent: 06706291.9/EP 1 845 961 B1, "Treatment of Thromboembolic Disorders With Rivaroxaban," (January 22, 2016), Opponent: Hexal AG, pp. 1-12.	

Receipt date: 08/05/2016	Application Number	11883218	11883218 - GAU: 1627
INFORMATION DISCLOSURE STATEMENT BY APPLICANT	Filing Date	2008-07-16	
(Not for submission under 37 CFR 1.99)	First Named Inventor	Frank MISSELWITZ et al.	
	Art Unit	1627	
	Examiner Name	KAROL, JODY LYNN	
	Attorney Docket Number	0081565-000006	

/J.K./	12	Opposition, Application/Patent: 06706291.9/EP 1 845 961 B1, "Treatment of Thromboembolic Disorders With Rivaroxaban," (January 22, 2016), Opponent: Kraus&Weisert, pp. 1-11.	
/J.K./	13	Opposition, Application/Patent: 06706291.9/EP 1 845 961 B1, "Treatment of Thromboembolic Disorders With Rivaroxaban," (January 22, 2016), Opponent: Stolmár & Partner IP, pp. 1-9.	
/J.K./	14	AULTON, "Pharmaceutics The Science of Dosage Form Design," Second Edition, Churchill Livingstone, (2002), pp. 410-411.	
/J.K./	15	LIEBERMAN et al., "Pharmaceutical Dosage Forms Tablets," Second Edition, Revised and Expanded, Marcel Dekker, Inc., (1989), page. 131. (3 Pages).	
/J.K./	16	FOSTER et al., "Basic Pharmacology," University of Manchester, Department of Pharmacology, Materia Medica and Therapeutics, (1980), pp. 255 (3 pages)	
/J.K./	17	Xarelto Dosing and Transition Management, Janssen Pharmaceuticals, Inc., (April 2015), pp. 1-3	
/J.K./	18	GOODMAN & GILMAN'S, "The Pharmacological Basis of Therapeutics," 10th Edition, (edited by Joel G. Hardman, Lee E. Limbird, Alfred Goodman Gilman, Chapter 1, (2001), pp. 1-29.	
/J.K./	19	ROTE LISTE, (2004), Clexane (Enoxaparin-Natrium), pp. 20. (3 pages)	
/J.K./	20	KUBITZA et al., "Multiple does Escalation Study Investigating BAY 59-7939 an Oral, Direct Factor Xa Inhibitor - in Healthy Male Subjects," (PO080), Pathophysiol Haemost Thromb, (2003), Vol. 33 (suppl2), pp. 98.	
/J.K./	21	KUBITZA et al., "Single dose Escalation Study of BAY 59-7939 - an Oral, Direct Factor Xa Inhibitor - in Healthy Male Subjects," (PO081), Pathophysiol Haemost Thromb, (2003), Vol. 33 (suppl2), pp. 98.	
/J.K./	22	FAREED et al., "Pharmacodynamic and Pharmacokinetic Properties of Enoxaparin," Clin Pharmacokinet, (2003), Vol. 42, No. 12, pp. 1043-1057.	

Receipt date: 08/05/2016	Application Number	11883218 11883218 - GAU: 1627
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**	Filing Date	2008-07-16
	First Named Inventor	Frank MISSELWITZ et al.
	Art Unit	1627
	Examiner Name	KAROL, JODY LYNN
	Attorney Docket Number	0081565-000006

/J.K./	23	HARDER et al., "Effects of BAY 59-7939, an Innovative, Oral, Direct Factor Xa Inhibitor, on Thrombin Generation in Healthy Volunteers," (PO078), Pathophysiol Haemost Thromb, (2003), Vol. 33 (suppl2), pp. 97.	
/J.K./	24	RITSCHEL et al., "Die Tablette Handbuch der Entwicklung, Herstellung und Qualitätssicherung," Aulendorf: ECV - Editio-Cantor-Verl., (2002). 3 pages.	
/J.K./	25	KEARON, "Duration of Venous Thromboembolism Prophylaxis After Surgery," CHEST (2003), Vol. 124, pp. 386S-392S.	
/J.K./	26	DERENDORF et al., "Pharmakokinetik Einführung in die Theorie und Relevanz Für die Arzneimitteltherapie," Wissenschaftliche Verlagsgesellschaft mbH Stuttgart, (2002), pp. 1-23.	
/J.K./	27	WEINZ et al., "In Vitro Metabolism of Bay 59-7939-An Oral, Direct Factor Xa Inhibitor," (195), Drug Metabolism Review, (2004), Vol. 36, Issue 1 Supplement, Abstracts from the 7th International ISSX Meeting, pp. 98.	
/J.K./	28	VRIJENS et al., "Non-Vitamin K Antagonist Oral Anticoagulants: Considerations on Once- Vs. Twice-Daily Regimens and their Potential Impact on Medication Adherence," Europace, (2015), Vol. 17, pp. 514-523.	
/J.K./	29	OBERPICHLER-SCHWENK: "Rivaroxaban", Medizinische Monatsschrift für Pharmazeuten, (2008), Vol. 31, No. 11, pp. 412-416.	
/J.K./	30	European Pharmacopeia, 5th edition, 15 June 2004, 2.9.3 Dissolution Test for Solid Dosage Forms, pp. 1-4.	
/J.K./	31	BIRKETT, "Pharmacokinetics made easy 11 Designing dose Regimens," Aust Prescr, (1996), Vol. 19, pp. 76-79. (6 pages)	
/J.K./	32	Hospira UK Ltd and Genentech Inc, dated 10th April 2014, Neutral Citation No. [2014] EWHC 1094 (Pat), pp. 1-47.	
/J.K./	33	EU Clinical Trials Register, EudraCT Number 2004-002171-16 (Sweden), 17 November 2004, https:/ /www.clinicaltrialsregister.eu/ctr-search/trial/2004-002171-16/SE, pp. 1-5.	

Receipt date: 08/05/2016	Application Number	11883218	11883218 - GAU: 1627
INFORMATION DISCLOSURE STATEMENT BY APPLICANT	Filing Date	2008-07-16	
(Not for submission under 37 CFR 1.99)	First Named Inventor	Frank MISSELWITZ et al.	
	Art Unit	1627	
	Examiner Name	KAROL, JODY LYNN	
	Attorney Docket Number	0081565-000006	

/J.K./	34	ROWLAND et al., "Clinical Pharmacokinetics, concepts and applications", 3rd Edition, Lea and Febiger, Philadelphia (1995), (Why Clinical Pharmacokinetics?), pp.1-7.	
/J.K./	35	PATRONO et al., "Platelet-Active Drugs The Relationships among Dose, Effectiveness, and Side Effects," CHEST, (January 2001), Vol. 119, No. 1, pp. 39S-63S.	
/J.K./	36	MUECK et al., "Clinical Pharmacokinetic and Pharmacodynamic Profile of Rivaroxaban," Clin Pharmacokinet, (2014), Vol. 53, pp. 1-16.	
/J.K./	37	ClinicalTrials.gov, "Dose-ranging Study of Once-daily Regimen of BAY 59-7939 in the Prevention of VTE in Patients Undergoing Elective Total Hip Replacement (ODIXaHIP-0D), https://clinicaltrials.gov/ct2/show/study/NCT00396786#wrapper, pp. 1-3; accessed Nov. 1, 2016.	
/J.K./	38	CHARBONNIER et al., "Comparison of a once daily with a twice daily subcutaneous low molecular weight heparin regimen in the treatment of deep vein thrombosis. FRAXODI group," Thromb Haemost, (May 1998), Vol. 79, No. 5, pp. 897-901. (Abstract Only)	
/J.K./	39	TURPIE et al., "BAY 59-7939: an Oral, Direct Factor Xa Inhibitor for the Prevention of Venous Thromboembolism in Patients after total Knee Replacement. A Phase II Dose-Ranging Study," Journal of Thrombosis and Haemostasis, (2005), Vol. 3, pp. 2479-2486.	
/J.K./	40	KUBITZA et al., "Safety, Pharmacodynamics, and Pharmacokinetics of Single Doses of BAY 59-7939, an Oral, Direct Factor Xa Inhibitor," Clinical Pharmacology & Therapeutics, (2005), Vol. 78, No. 4, pp. 412-421.	
/J.K./	41	GRIFFIN et al., "The Textbook pf Pharmaceutical Medicine," 4th Edition, BMJ Books (2002), pp. 225-226, 238-239. (6 pages)	
/J.K./	42	U.S. Pharmacopeia, General Chapters: <1088> IN VITRO AND IN VIVO EVALUATION OF DOSAGE FORMS, http:/ /www.pharmacopeia.cn/v29240/usp29nf24s0_cl088.htm, pp. 1-17; accessed Jan. 21, 2016.	
/J.K./	43	HARRON et al., "Bopindolol A Review of its Pharmacodynamic and Pharmacokinetic Properties and Therapeutic Efficacy," Drugs, (1991), Vol. 41, No. 1, pp. 130-149.	
/J.K./	44	Clinical Pharmacology and Biopharmaceutics Review(s), CENTER FOR DRUG EVALUATION AND RESEARCH, Application No. 0224060rig1s000; 2009, pp. 1-139.	

Receipt date: 08/05/2016	Application Number	11883218 11883218 - GAU: 1627
INFORMATION DISCLOSURE STATEMENT BY APPLICANT	Filing Date	2008-07-16
(Not for submission under 37 CFR 1.99)	First Named Inventor	Frank MISSELWITZ et al.
	Art Unit	1627
	Examiner Name	KAROL, JODY LYNN
	Attorney Docket Number	0081565-000006

/J.K./	45	Cleveland Clinic Pharmacotherapy Update, "Enoxaparin Clinical Pearl", Vol. VI, No. 1, January/February 2003, http://www.clevelandclinicmeded.com/medicalpubs/pharmacy/janfeb2003/enoxaparin.htm, pp. 1-2.	
/J.K./	46	FAREED et al., "Studies on the Mechanism of Action of BAY 59-7939 - an Oral, Direct Factor Xa Inhibitor," (PO077), Pathophysiol Haemost Thromb, (2003), Vol. 33 (suppl2), pp. 97.	
/J.K./	47	LIEBERMAN et al., "Pharmaceutical Dosage Forms," Tablets, (1980), Vol. 1, Marcel Dekker, pp.172-181; (7 pages)	
/J.K./	48	MATTSSON: "Pharmaceutical Binders and Their Function in Directly Compressed Tablets — Mechanistic Studies on the Effect of Dry Binders on Mechanical Strength, Pore Structure and Disintegration of Tablets"; Comprehensive Summaries of Uppsala Dissertations from the Faculty of Pharmacy, 238, ACTA Universitatis Upsaliensis Uppsala 2000, pp.1-62.	
/J.K./	49	RASENACK et al., "Crystal Habit and Tableting Behavior," International Journal of Pharmaceutics, (2002), Vol. 244, pp. 45-57.	

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature	/Jody Karol/	Date Considered	08/17/2016

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11883218	MISSELWITZ ET AL.
	Examiner	**Art Unit**
	Jody L Karol	1627

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	11/02/2010	03/09/2011	09/08/2011	08/22/2016					
1	1	÷	✓	✓	=					
	2	÷	✓	-	-					
	3	÷	N	-	-					
	4	÷	✓	✓	-					
	5	÷	✓	✓	-					
	6	÷	✓	-	-					
	7	÷	N	N	-					
	8	÷	N	N	-					
	9		✓	N	-					
	10		✓	-	-					
	11		✓	✓	-					
	12		✓	-	-					
	13		✓	-	-					
	14		✓	-	-					
	15			N	-					
	16			N	-					
2	17			N	=					
3	18			✓	=					
4	19			N	=					

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11883218	MISSELWITZ ET AL.
	Examiner	Art Unit
	JODY KAROL	1627

CPC- SEARCHED		
Symbol	Date	Examiner
A61K 31/00; 31/5377	8/22/2016	JLK

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
514	230.8; 236.8 (see attached)	3/9/2011	JLK
	updated (see attached)	9/8/2011	JLK

SEARCH NOTES		
Search Notes	Date	Examiner
Inventor Search in EAST/PALM	3/9/2011	JLK
EAST Keyword Search (see attached)	3/9/2011	JLK
STIC Search (see attached)	2/17/2011	JLK
STN Search (see attached)	3/9/2011	JLK
Inventor and EAST Search updated (see attached)	9/8/2011	JLK
Inventor and EAST Search updated (see attached)	8/22/2016	JLK
EAST Keyword Search updated	8/22/2016	JLK

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
A61K	31/00; 31/5377	8/22/2016	JLK

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	160	(Misslewitz, Frank).in. or (Kubitza, Dagmar).in. or (Park, Son-Mi).in. or (Wehling, Klaus).in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2016/08/22 13:41
L2	433	BAY 59-7939	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2016/08/22 13:41
L3	1892	rivaroxaban$3	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2016/08/22 13:41
L4	15689	(deep vein thrombos$2) or (deep venous thrombos$2)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2016/08/22 13:41
L5	2218	L4 and (Xa near3 inhibitor)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2016/08/22 13:41
L6	146	L4 and (direct factor Xa inhibitor)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2016/08/22 13:41
L7	98	L4 and ($thiophenecarboxamide)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2016/08/22 13:41
L8	1	"20090004265".pn.	US-PGPUB	ADJ	ON	2016/08/22 13:42
L9	82716	(A61K31/00 OR A61K31/5377).CPC.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2016/08/22 13:51
L10	5965	L9 and (L4 or stroke or pulmonary embolism)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2016/08/22 13:51
L11	1278	L9 and (L4 or stroke or pulmonary embolism).ti,ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2016/08/22 13:52
L12	26462	(A61K31/5377).CPC.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2016/08/22 13:52
L13	611	L12 and (L4 or stroke or pulmonary embolism).ti,ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO;	ADJ	ON	2016/08/22 13:52

			JPO; DERWENT; IBM_TDB			
L14	22	L9 and (L4 or stroke or pulmonary embolism).ti,ab. and rivaroxaban$3	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2016/08/22 13:52

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L15	6923	(A61K31/00 OR A61K31/5377).CPC.	USPAT	ADJ	ON	2016/08/22 13:52
L16	2236	(A61K31/5377).CPC.	USPAT	ADJ	ON	2016/08/22 13:53
L17	0	L16 and ((deep vein thrombos$2) or (deep venous thrombos$2) or stroke or pulmonary embolism).ti,ab. and rivaroxaban$3	USPAT	ADJ	ON	2016/08/22 13:53
L18	20	L16 and ((deep vein thrombos$2) or (deep venous thrombos$2) or stroke or pulmonary embolism).ti,ab.	USPAT	ADJ	ON	2016/08/22 13:54

8/ 22/ 2016 1:54:18 PM
C:\ Users\ jkarol\ Documents\ EAST\ Workspaces\ 11883218 - Prevention and Method of Treatment of Thromboembolic Disorders.wsp

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11883218	MISSELWITZ ET AL.
	Examiner	**Art Unit**
	JODY KAROL	1627

CPC						
Symbol					**Type**	**Version**
A61K		31	/	00	F	2013-01-01
A61K		31	/	5377	I	2013-01-01
			/			
			/			
			/			
			/			
			/			
			/			
			/			
			/			
			/			
			/			
			/			
			/			

CPC Combination Sets							
Symbol					**Type**	**Set**	**Ranking**	**Version**
			/					
			/					

/JODY KAROL/ Examiner.Art Unit 1627	08/22/2016	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	4	
/SREENI PADMANABHAN/ Supervisory Patent Examiner.Art Unit 1627	08/22/2016	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11883218	MISSELWITZ ET AL.
	Examiner	**Art Unit**
	JODY KAROL	1627

US ORIGINAL CLASSIFICATION		INTERNATIONAL CLASSIFICATION										
CLASS	SUBCLASS	CLAIMED					NON-CLAIMED					
		A	6	1	K	31 / 00 (2006.01.01)						
CROSS REFERENCE(S)		A	6	1	K	31 / 5377 (2006.01.01)						
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)											

/JODY KAROL/ Examiner.Art Unit 1627	08/22/2016	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	4	
/SREENI PADMANABHAN/ Supervisory Patent Examiner.Art Unit 1627	08/22/2016	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11883218	MISSELWITZ ET AL.
	Examiner	**Art Unit**
	JODY KAROL	1627

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	1	2	17												
	2	3	18												
	3	4	19												
	4														
	5														
	6														
	7														
	8														
	9														
	10														
	11														
	12														
	13														
	14														
	15														
	16														

/JODY KAROL/ Examiner.Art Unit 1627 (Assistant Examiner)	08/22/2016 (Date)	**Total Claims Allowed:** 4	
/SREENI PADMANABHAN/ Supervisory Patent Examiner.Art Unit 1627 (Primary Examiner)	08/22/2016 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure none

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	11883218
Filing Date	2008-07-16
First Named Inventor	Frank MISSELWITZ et al.
Art Unit	1627
Examiner Name	KAROL, JODY LYNN
Attorney Docket Number	0081565-000006

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Patent citation information please click the Add button. Add

U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	11883218
	Filing Date	2008-07-16
	First Named Inventor	Frank MISSELWITZ et al.
	Art Unit	1627
	Examiner Name	KAROL, JODY LYNN
	Attorney Docket Number	0081565-000006

	1	Substantiation of the Opposition, Application/Patent: 06706291.9/EP 1 845 961 B1, "Treatment of Thromboembolic Disorders With Rivaroxaban," (December 30, 2015), Henkel, Breuer & Partner, pp. 1-25.	
	2	Statement of Opposition, Application/Patent: 06706291.9/EP 1 845 961 B1, "Treatment of Thromboembolic Disorders With Rivaroxaban," (January 6, 2016), Elkington and Fife LLP, Opponent: Actavis Group PTC ehf, pp. 1-12.	
	3	Notice of Opposition to a European Patent, Application/Patent: 06706291.9/EP 1 845 961 B1, "Treatment of Thromboembolic Disorders With Rivaroxaban," (January 21, 2016), Opponent: Abdi Ibrahim Ilac Sanayi ve Ticaret A.S., pp. 1-9.	
	4	Statement of Grounds for Opposition, Application/Patent: 06706291.9/EP 1 845 961 B1, "Treatment of Thromboembolic Disorders With Rivaroxaban," (January 21, 2016), Opponent: Generics Ltd.; Elend, Almut Susanne Authorised Representative, pp. 1-10.	
	5	The Opposition patent, Application/Patent: 06706291.9/EP 1 845 961 B1, "Treatment of Thromboembolic Disorders With Rivaroxaban," (January 21, 2016), Opponent: Alexander Wittkopp, pp. 1-14.	
	6	Opposition, Application/Patent: 06706291.9/EP 1 845 961 B1, "Treatment of Thromboembolic Disorders With Rivaroxaban," (January 21, 2016), Opponent: STADA Arzneimittel AG, and an English Translation, pp. 1-27.	
	7	Opposition, Application/Patent: 06706291.9/EP 1 845 961 B1, "Treatment of Thromboembolic Disorders With Rivaroxaban," (January 21, 2016), Opponent: Teva Pharmaceutical Industries Ltd, pp. 1-14.	
	8	Statement of Opposition, Application/Patent: 06706291.9/EP 1 845 961 B1, "Treatment of Thromboembolic Disorders With Rivaroxaban," (January 21, 2016), Opponent: Zaklady Farmaceutyczne Polpharma SA, pp.1-12.	
	9	Opposition, Application/Patent: 06706291.9/EP 1 845 961 B1, "Treatment of Thromboembolic Disorders With Rivaroxaban," (January 22, 2016), Opponent: ABG Patentes, S.L., pp. 1-22.	
	10	Opposition, Application/Patent: 06706291.9/EP 1 845 961 B1, "Treatment of Thromboembolic Disorders With Rivaroxaban," (January 22, 2016), Opponent: Galenicum Health S.L., pp. 1-19.	
	11	Opposition, Application/Patent: 06706291.9/EP 1 845 961 B1, "Treatment of Thromboembolic Disorders With Rivaroxaban," (January 22, 2016), Opponent: Hexal AG, pp. 1-12.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	11883218
	Filing Date	2008-07-16
	First Named Inventor	Frank MISSELWITZ et al.
	Art Unit	1627
	Examiner Name	KAROL, JODY LYNN
	Attorney Docket Number	0081565-000006

	12	Opposition, Application/Patent: 06706291.9/EP 1 845 961 B1, "Treatment of Thromboembolic Disorders With Rivaroxaban," (January 22, 2016), Opponent: Kraus&Weisert, pp. 1-11.	
	13	Opposition, Application/Patent: 06706291.9/EP 1 845 961 B1, "Treatment of Thromboembolic Disorders With Rivaroxaban," (January 22, 2016), Opponent: Stolmár & Partner IP, pp. 1-9.	
	14	AULTON, "Pharmaceutics The Science of Dosage Form Design," Second Edition, Churchill Livingstone, (2002), pp. 410-411.	
	15	LIEBERMAN et al., "Pharmaceutical Dosage Forms Tablets," Second Edition, Revised and Expanded, Marcel Dekker, Inc., (1989), page. 131. (3 Pages).	
	16	FOSTER et al., "Basic Pharmacology," University of Manchester, Department of Pharmacology, Materia Medica and Therapeutics, (1980), pp. 255 (3 pages)	
	17	Xarelto Dosing and Transition Management, Janssen Pharmaceuticals, Inc., (April 2015), pp. 1-3	
	18	GOODMAN & GILMAN'S, "The Pharmacological Basis of Therapeutics," 10th Edition, (edited by Joel G. Hardman, Lee E. Limbird, Alfred Goodman Gilman, Chapter 1, (2001), pp. 1-29.	
	19	ROTE LISTE, (2004), Clexane (Enoxaparin-Natrium), pp. 20. (3 pages)	
	20	KUBITZA et al., "Multiple does Escalation Study Investigating BAY 59-7939 an Oral, Direct Factor Xa Inhibitor - in Healthy Male Subjects," (PO080), Pathophysiol Haemost Thromb, (2003), Vol. 33 (suppl2), pp. 98.	
	21	KUBITZA et al., "Single dose Escalation Study of BAY 59-7939 - an Oral, Direct Factor Xa Inhibitor - in Healthy Male Subjects," (PO081), Pathophysiol Haemost Thromb, (2003), Vol. 33 (suppl2), pp. 98.	
	22	FAREED et al., "Pharmacodynamic and Pharmacokinetic Properties of Enoxaparin," Clin Pharmacokinet, (2003), Vol. 42, No. 12, pp. 1043-1057.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	11883218
	Filing Date	2008-07-16
	First Named Inventor	Frank MISSELWITZ et al.
	Art Unit	1627
	Examiner Name	KAROL, JODY LYNN
	Attorney Docket Number	0081565-000006

	23	HARDER et al., "Effects of BAY 59-7939, an Innovative, Oral, Direct Factor Xa Inhibitor, on Thrombin Generation in Healthy Volunteers," (PO078), Pathophysiol Haemost Thromb, (2003), Vol. 33 (suppl2), pp. 97.	
	24	RITSCHEL et al., "Die Tablette Handbuch der Entwicklung, Herstellung und Qualitätssicherung," Aulendorf: ECV - Editio-Cantor-Verl., (2002). 3 pages.	
	25	KEARON, "Duration of Venous Thromboembolism Prophylaxis After Surgery," CHEST (2003), Vol. 124, pp. 386S-392S.	
	26	DERENDORF et al., "Pharmakokinetik Einführung in die Theorie und Relevanz Für die Arzneimitteltherapie," Wissenschaftliche Verlagsgesellschaft mbH Stuttgart, (2002), pp. 1-23.	
	27	WEINZ et al., "In Vitro Metabolism of Bay 59-7939-An Oral, Direct Factor Xa Inhibitor," (195), Drug Metabolism Review, (2004), Vol. 36, Issue 1 Supplement, Abstracts from the 7th International ISSX Meeting, pp. 98.	
	28	VRIJENS et al., "Non-Vitamin K Antagonist Oral Anticoagulants: Considerations on Once- Vs. Twice-Daily Regimens and their Potential Impact on Medication Adherence," Europace, (2015), Vol. 17, pp. 514-523.	
	29	OBERPICHLER-SCHWENK: "Rivaroxaban", Medizinische Monatsschrift für Pharmazeuten, (2008), Vol. 31, No. 11, pp. 412-416.	
	30	European Pharmacopeia, 5th edition, 15 June 2004, 2.9.3 Dissolution Test for Solid Dosage Forms, pp. 1-4.	
	31	BIRKETT, "Pharmacokinetics made easy 11 Designing dose Regimens," Aust Prescr, (1996), Vol. 19, pp. 76-79. (6 pages)	
	32	Hospira UK Ltd and Genentech Inc, dated 10th April 2014, Neutral Citation No. [2014] EWHC 1094 (Pat), pp. 1-47.	
	33	EU Clinical Trials Register, EudraCT Number 2004-002171-16 (Sweden), 17 November 2004, https:/ /www.clinicaltrialsregister.eu/ctr-search/trial/2004-002171-16/SE, pp. 1-5.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	11883218
	Filing Date	2008-07-16
	First Named Inventor	Frank MISSELWITZ et al.
	Art Unit	1627
	Examiner Name	KAROL, JODY LYNN
	Attorney Docket Number	0081565-000006

	34	ROWLAND et al., "Clinical Pharmacokinetics, concepts and applications", 3rd Edition, Lea and Febiger, Philadelphia (1995), (Why Clinical Pharmacokinetics?), pp.1-7.	
	35	PATRONO et al., "Platelet-Active Drugs The Relationships among Dose, Effectiveness, and Side Effects," CHEST, (January 2001), Vol. 119, No. 1, pp. 39S-63S.	
	36	MUECK et al., "Clinical Pharmacokinetic and Pharmacodynamic Profile of Rivaroxaban," Clin Pharmacokinet, (2014), Vol. 53, pp. 1-16.	
	37	ClinicalTrials.gov, "Dose-ranging Study of Once-daily Regimen of BAY 59-7939 in the Prevention of VTE in Patients Undergoing Elective Total Hip Replacement (ODIXaHIP-0D), https://clinicaltrials.gov/ct2/show/study/NCT00396786#wrapper, pp. 1-3; accessed Nov. 1, 2016.	
	38	CHARBONNIER et al., "Comparison of a once daily with a twice daily subcutaneous low molecular weight heparin regimen in the treatment of deep vein thrombosis. FRAXODI group," Thromb Haemost, (May 1998), Vol. 79, No. 5, pp. 897-901. (Abstract Only)	
	39	TURPIE et al., "BAY 59-7939: an Oral, Direct Factor Xa Inhibitor for the Prevention of Venous Thromboembolism in Patients after total Knee Replacement. A Phase II Dose-Ranging Study," Journal of Thrombosis and Haemostasis, (2005), Vol. 3, pp. 2479-2486.	
	40	KUBITZA et al., "Safety, Pharmacodynamics, and Pharmacokinetics of Single Doses of BAY 59-7939, an Oral, Direct Factor Xa Inhibitor," Clinical Pharmacology & Therapeutics, (2005), Vol. 78, No. 4, pp. 412-421.	
	41	GRIFFIN et al., "The Textbook pf Pharmaceutical Medicine," 4th Edition, BMJ Books (2002), pp. 225-226, 238-239. (6 pages)	
	42	U.S. Pharmacopeia, General Chapters: <1088> IN VITRO AND IN VIVO EVALUATION OF DOSAGE FORMS, http:/ /www.pharmacopeia.cn/v29240/usp29nf24s0_cl088.htm, pp. 1-17; accessed Jan. 21, 2016.	
	43	HARRON et al., "Bopindolol A Review of its Pharmacodynamic and Pharmacokinetic Properties and Therapeutic Efficacy," Drugs, (1991), Vol. 41, No. 1, pp. 130-149.	
	44	Clinical Pharmacology and Biopharmaceutics Review(s), CENTER FOR DRUG EVALUATION AND RESEARCH, Application No. 0224060rig1s000; 2009, pp. 1-139.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	11883218
	Filing Date	2008-07-16
	First Named Inventor	Frank MISSELWITZ et al.
	Art Unit	1627
	Examiner Name	KAROL, JODY LYNN
	Attorney Docket Number	0081565-000006

	45	Cleveland Clinic Pharmacotherapy Update, "Enoxaparin Clinical Pearl", Vol. VI, No. 1, January/February 2003, http://www.clevelandclinicmeded.com/medicalpubs/pharmacy/janfeb2003/enoxaparin.htm, pp. 1-2.
	46	FAREED et al., "Studies on the Mechanism of Action of BAY 59-7939 - an Oral, Direct Factor Xa Inhibitor," (PO077), Pathophysiol Haemost Thromb, (2003), Vol. 33 (suppl2), pp. 97.
	47	LIEBERMAN et al., "Pharmaceutical Dosage Forms," Tablets, (1980), Vol. 1, Marcel Dekker, pp.172-181; (7 pages)
	48	MATTSSON: "Pharmaceutical Binders and Their Function in Directly Compressed Tablets — Mechanistic Studies on the Effect of Dry Binders on Mechanical Strength, Pore Structure and Disintegration of Tablets"; Comprehensive Summaries of Uppsala Dissertations from the Faculty of Pharmacy, 238, ACTA Universitatis Upsaliensis Uppsala 2000, pp.1-62.
	49	RASENACK et al., "Crystal Habit and Tableting Behavior," International Journal of Pharmaceutics, (2002), Vol. 244, pp. 45-57.

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	11883218
	Filing Date	2008-07-16
	First Named Inventor	Frank MISSELWITZ et al.
	Art Unit	1627
	Examiner Name	KAROL, JODY LYNN
	Attorney Docket Number	0081565-000006

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Christine M. Hansen/	Date (YYYY-MM-DD)	2016-08-05
Name/Print	Christine M. Hansen	Registration Number	40,634

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Patent Application Fee Transmittal

Application Number:	11883218
Filing Date:	16-Jul-2008
Title of Invention:	Prevention and Treatment of Thromboembolic Disorders
First Named Inventor/Applicant Name:	Frank Misselwitz
Filer:	Christine Hansen/Mich Sok
Attorney Docket Number:	11987-00042

Filed as Large Entity

Filing Fees for U.S. National Stage under 35 USC 371

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**180**

Electronic Acknowledgement Receipt

EFS ID:	26556295
Application Number:	11883218
International Application Number:	
Confirmation Number:	9960
Title of Invention:	Prevention and Treatment of Thromboembolic Disorders
First Named Inventor/Applicant Name:	Frank Misselwitz
Customer Number:	21839
Filer:	Christine Hansen/Mich Sok
Filer Authorized By:	Christine Hansen
Attorney Docket Number:	11987-00042
Receipt Date:	05-AUG-2016
Filing Date:	16-JUL-2008
Time Stamp:	09:11:41
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$180
RAM confirmation Number	080516INTEFSW09130600
Deposit Account	8390
Authorized User	Mich Sok

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

37 CFR 1.17 (Patent application and reexamination processing fees)

37 CFR 1.19 (Document supply fees)

37 CFR 1.20 (Post Issuance fees)

37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	IDS_TL.pdf	7415998 ef29c71aeb8f888314803979956d45b9d16f8aaa	no	6
Warnings:					
Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	PTO_SB08.PDF	616183 f3ec9499c683e5272a09c3e954c440be1c362bdd	no	8
Warnings:					
Information:					
A U.S. Patent Number Citation or a U.S. Publication Number Citation is required in the Information Disclosure Statement (IDS) form for autoloading of data into USPTO systems. You may remove the form to add the required data in order to correct the Informational Message if you are citing U.S. References. If you chose not to include U.S. References, the image of the form will be processed and be made available within the Image File Wrapper (IFW) system. However, no data will be extracted from this form. Any additional data such as Foreign Patent Documents or Non Patent Literature will be manually reviewed and keyed into USPTO systems.					
3	Non Patent Literature	NPL1_20151230_Opposition_Substantiation_Henkel-Breuer_O01.pdf	3112352 1e63f1131820649031562cb4dd3f6479b05f12c3	no	25
Warnings:					
Information:					
4	Non Patent Literature	NPL2_20160106_Opposition_Actavis_O02.pdf	1356624 853469400e0159ffa4b37243e3fa59f94121587e	no	12
Warnings:					
Information:					
5	Non Patent Literature	NPL3_20160121_Opposition_Abdi-Ibrahim_O07.pdf	791944 7b870c8dda17c1920e0383d818b5543a31d2af43	no	9
Warnings:					
Information:					

6	Non Patent Literature	NPL4_20160121_Opposition_Generics_Ltd_O06.pdf	1193505 6005e685e9cfd0f18ac1e38712cdb0da1a831b3a	no	10
Warnings:					
Information:					
7	Non Patent Literature	NPL5_20160121_Opposition_Hamm-Wittkopp_O08.pdf	1589689 663a01d949a82b14177e75d8cd68b3d11ec30ef3	no	14
Warnings:					
Information:					
8	Non Patent Literature	NPL6_20160121_Opposition_Stada_O05.pdf	1900207 61c7e966f137f78c1bbac67b9c0e5b62afb623e5	no	27
Warnings:					
Information:					
9	Non Patent Literature	NPL7_20160121_Opposition_Teva_O04.pdf	2317692 051d0a6632dc24a3aa0da73dbd229560cd488078	no	14
Warnings:					
Information:					
10	Non Patent Literature	NPL8_20160121_Opposition_Zaklady_O03.pdf	1357184 dcf0090f1fd16c4c42b69becd643fb1c0371bcd4	no	12
Warnings:					
Information:					
11	Non Patent Literature	NPL9_20160122_Opposition_ABG-Patentes_O10.pdf	2729518 243ea2bc2998a5f4e0de963587baaa7948ebf19c	no	22
Warnings:					
Information:					
12	Non Patent Literature	NPL10_20160122_Opposition_Galenicum_Health_O09.pdf	3478479 7d67966635400e557de6771ff037d7d2b1e2f1f4	no	19
Warnings:					
Information:					

13	Non Patent Literature	NPL11_20160122_Opposition_Hexal_O12.pdf	1565224 a83897f076dbd16ef6126a12d26859762730d241	no	12
Warnings:					
Information:					
14	Non Patent Literature	NPL12_20160122_Opposition_Kraus-Weisert_O13.pdf	1353140 ca262515e02a019040f513b0b335ab1a7c3d8151	no	11
Warnings:					
Information:					
15	Non Patent Literature	NPL13_20160122_Opposition_Stolmar_O11.pdf	985624 53dbbb3147c201cef63607be7483b7a6a029ed7e	no	9
Warnings:					
Information:					
16	Non Patent Literature	NPL14_AULTON.pdf	943683 2a693799c7000715a892c5f6cef6f8c7900b8a5f	no	4
Warnings:					
Information:					
17	Non Patent Literature	NPL15_LIEBERMAN.pdf	603894 80aca18da9b44201265d5a86f25614bb6c286a1f	no	3
Warnings:					
Information:					
18	Non Patent Literature	NPL16_FOSTER.pdf	346600 73cc576b83bc48c955b31b6a28d145381c0fb997	no	3
Warnings:					
Information:					
19	Non Patent Literature	NPL17_Xarelto_Dosing_and_Transition_Management_Janssen.pdf	1175221 2df52b15bbde85fb54db321ef7421bb0b34e7b0e	no	3
Warnings:					
Information:					

20	Non Patent Literature	NPL18_GOODMAN.pdf	9177699 b48b18e4bcfe5c2bcd763c8265f04239e578a5f0	no	30
Warnings:					
Information:					
21	Non Patent Literature	NPL19_Rote_Liste_2004_Clexane.pdf	737387 594d000d7e0b0aa1060e33c2e5a6e4ed5fcc7b2e	no	3
Warnings:					
Information:					
22	Non Patent Literature	NPL20_KUBITZA.pdf	351299 037f8d1362ea64996ddef0a78aecb800d558ba5e	no	1
Warnings:					
Information:					
23	Non Patent Literature	NPL21_KUBITZA.pdf	351484 cceba98c186769036aa6c38ecdab5cabba6224c9	no	1
Warnings:					
Information:					
24	Non Patent Literature	NPL22_FAREED.pdf	3771391 1621f960e2c7da9b7f3b19066e483ecdd4517329	no	15
Warnings:					
Information:					
25	Non Patent Literature	NPL23_HARDER.pdf	370096 b97f7eb4781c47f44ecc20e41fd4f8332f9d5845	no	1
Warnings:					
Information:					
26	Non Patent Literature	NPL24_RITSCHEL.pdf	408998 61e942bcb057f4579c3f5c635c5219b5b0a5e296	no	3
Warnings:					
Information:					

27	Non Patent Literature	NPL25_KEARON.pdf	1831093 4fa524e79800bdfc40b0240919237ba292e6ae6e	no	7
Warnings:					
Information:					
28	Non Patent Literature	NPL26_DERENDORF.pdf	8690726 7985600b4e6d120be85eb3a49a08e81df6086657	no	23
Warnings:					
Information:					
29	Non Patent Literature	NPL27_WEINZ.pdf	1157213 0f682c146b971cc11dbc56457b88dfe6a6836d17	no	2
Warnings:					
Information:					
30	Non Patent Literature	NPL28_VRIJENS.pdf	2110898 527691183017caca850f7e3d25eafa2163e3312c	no	10
Warnings:					
Information:					
31	Non Patent Literature	NPL29_OBERPICHLER-SCHWENK.pdf	1341809 8619babd378325f29c93e205f495f5f74df526ce	no	5
Warnings:					
Information:					
32	Non Patent Literature	NPL30_European_Pharmacopeia.pdf	1174149 c8091d3f72185fda9cb481f52ca1442edd13264b	no	4
Warnings:					
Information:					
33	Non Patent Literature	NPL31_BIRKETT.pdf	682326 648532e4ab77fa7ae875b6c038d92cf8d03ccb1e	no	6
Warnings:					
Information:					

34	Non Patent Literature	NPL32_Hospira_Genentech.pdf	7440283 c32ad09f572d1370f0be873a18ca82b287a54bad	no	47
Warnings:					
Information:					
35	Non Patent Literature	NPL33_EU_Clinical_Trials.pdf	642202 8bf6833477260d9161b86870708b7a449513a70a	no	5
Warnings:					
Information:					
36	Non Patent Literature	NPL34_ROWLAND.pdf	1188754 4fae94d178f9b457c6a825a46b852c6ae261b799	no	7
Warnings:					
Information:					
37	Non Patent Literature	NPL35_PATRONO.pdf	6730746 398e74e040ff7064d107ef8047adf9c1f483e328	no	25
Warnings:					
Information:					
38	Non Patent Literature	NPL36_MUECK.pdf	3523653 26718c4782a3cb7168b98b443522ee84e978597a	no	16
Warnings:					
Information:					
39	Non Patent Literature	NPL37_ClinicalTrials.pdf	382939 b395dc0ea780d25b1b52a66316c68998205fd202	no	3
Warnings:					
Information:					
40	Non Patent Literature	NPL38_CHARBONNIER.pdf	132754 e89e133abac83eadf262a19ca9793dd758caed23	no	1
Warnings:					
Information:					

41	Non Patent Literature	NPL39_TURPIE.pdf	1668154 d89b8a902f0332771c40c4025d07c932f113a12f	no	8
Warnings:					
Information:					
42	Non Patent Literature	NPL40_KUBITZA.pdf	1787447 644abeac588d1bf86885c9a21b06f18de1291d80	no	10
Warnings:					
Information:					
43	Non Patent Literature	NPL41_GRIFFIN.pdf	611379 5b2f13641cedf6fddf9dffb6449b4d40375e4b5a	no	6
Warnings:					
Information:					
44	Non Patent Literature	NPL42_US_Pharmacopeia.pdf	4371380 3eb573b4ccfb1e3dee1d99de891d966bb91bb0b9	no	17
Warnings:					
Information:					
45	Non Patent Literature	NPL43_HARRON.pdf	5989726 cf0580e978303c30a39abe48bbdc404e78cd6c6d	no	20
Warnings:					
Information:					
46	Non Patent Literature	NPL44_Clinical_Pharmacology_Biopharmaceutics_Reviews_part_1.pdf	16544951 7e1e9484a6dccc80def7f0af811d72220ddd5c51	no	139
Warnings:					
Information:					
47	Non Patent Literature	NPL45_Cleveland_Clinic_Pharmacotherapy_Update.pdf	340371 72647dce41967b85705888fe1598dc2adc0b5d7b	no	2
Warnings:					
Information:					

48	Non Patent Literature	NPL46_FAREED.pdf	331746 69f6fe806793bb9992bb90966dac7935274b1178	no	1
Warnings:					
Information:					
49	Non Patent Literature	NPL47_LIEBERMAN.pdf	2761933 43cebfe0fe278d15bea7868c757a17032efbc5b7	no	7
Warnings:					
Information:					
50	Non Patent Literature	NPL48_MATTSSON.pdf	10521212 a2b3594986563f4c0475792b3354b8df072e24dc	no	62
Warnings:					
Information:					
51	Non Patent Literature	NPL49_RASENACK.pdf	2732950 872002d2188e3e66c1cddddc6200d7c33274edfb	no	13
Warnings:					
Information:					
52	Fee Worksheet (SB06)	fee-info.pdf	30305 99fc049e486119bc4ea8b32bdd67987770fbc138	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	134722214	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Frank Misselwitz et al.

Application No.: 11/883,218 Confirmation No.: 9960

Filed: July 16, 2008 Art Unit: 1627

For: PREVENTION AND TREATMENT OF THROMBOEMBOLIC DISORDERS Examiner: Karol, Jody Lynn

INFORMATION DISCLOSURE STATEMENT (IDS)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Pursuant to 37 C.F.R. §§1.56, 1.97 and 1.98, the attention of the Patent and Trademark Office is hereby directed to the references submitted herewith. It is respectfully requested that the information be expressly considered during the prosecution of this application, and that the references be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

This Information Disclosure Statement is filed before the mailing date of a final office action, a notice of allowance, or an action that otherwise closes prosecution in the application and is accompanied by the fee set forth in § 1.17(p). Accordingly, consideration is believed correct pursuant to 37 C.F.R. §1.97 (c).

The references cited today are copies of the grounds for Opposition and the references cited (that had not previously been cited) in thirteen Oppositions filed in a European counterpart application. To assist the Office with review, Applicants submit a list of the Oppositions identifying each by a number (e.g., O01, O02, etc.) and a cross-reference table. If any references are not in the English language, a brief statement of their relevancy may be found by cross-

referencing the reference against the Opposition where the reference was cited and determining the relevancy of the reference from the discussion of it in the English-language Opposition. In accordance with 37 CFR 1.98(a)(2)(ii), Applicant has not submitted copies of U.S. patents and U.S. patent applications. Applicant submits herewith copies of foreign patents and non-patent literature in accordance with 37 CFR 1.98(a)(2).

The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed for consideration of this paper herewith to our Deposit Account No. 02-4800, under Order No. 0081565-000006.

Dated: August 5, 2016

Respectfully submitted,

Electronic signature: /Christine M. Hansen/
Christine M. Hansen
Registration No.: 40,634
BUCHANAN INGERSOLL AND ROONEY PC
919 Market Street, Suite 1500
Wilmington, Delaware 19801-3046
(302) 552-4240
(302) 552-4295 (Fax)
Attorney for Applicant

Cross Reference Chart Showing Opponent's name followed by Opposition Number (e.g., O01, O02, etc.)

2015-12-30_Opposition-Substantiation_Henkel-Breuer_O01.pdf
2016-01-06_Opposition_Actavis_O02.pdf
2016-01-21_Opposition_Abdi-Ibrahim_O07.pdf
2016-01-21_Opposition_Generics_Ltd_O06.pdf
2016-01-21_Opposition_Hamm-Wittkopp_O08.pdf
2016-01-21_Opposition_Stada_O05.pdf
2016-01-21_Opposition_Teva_O04.pdf
2016-01-21_Opposition_Zaklady_O03.pdf
2016-01-22_Opposition_ABG-Patentes_O10.pdf
2016-01-22_Opposition_Galenicum_Health_O09.pdf
2016-01-22_Opposition_Hexal_O12.pdf
2016-01-22_Opposition_Kraus-Weisert_O13.pdf
2016-01-22_Opposition_Stolmar_O11.pdf

The following page has a cross-reference table associating each reference submitted with one or more of the above Oppositions with a reference number from the opposition in which they were cited.

Cross-reference table for consolidated document numbering in Oppositions against EP 1 845 961 B1

Consolidated Numbering	Reference	Publication Date	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13
D01	WO 2001/47919 A1; US 2003/153610	2001-07-05	HBP3	D1	D1	TM4	D1	D1	D1		D1	D1	E1/E9	D6	D6
D02	Kubitza et al., Blood, 2003, 102(11) Part 1 Abs 3004 [811a]	2003	HBP1	D2	D2	TM2a	D2	D2	D2	HW1	D2	D2	E2	D7	D1
D03	Kubitza et al., Blood, 2003, 102(11) Part 1 Abs 3010 [813a]	2003	HBP2	D3	D3	TM3	D3	D3	D3	HW2	D3	D3	E3		D2
D04	Pharmaceutics. The Science of Dosage Form Design, Second Edition, Ed. M.E. Aulton, 2002, pages 410-411	2002		D4	D4								E4		
D05	Pharmaceutical Dosage Forms: Tablets, Volume 1, Eds. H.A Lieberman et al., 1989, page 131	1989		D5	D5								E5		
D06	R. J. Leadley, Current Topics in Medicinal Chemistry 2001, 1 151-159 --- Coagulation Factor Xa Inhibition: Biological Background and Rationale	2001		D6	D6			D6					E6		
D07	R.W. Foster, Basic Pharmacology, 1980, page 255, Butterworths, University of Manchester	1980		D7	D7								E7		
D08	Xarelto® Dosing and transition management (PIL) Janssen Pharmaceuticals, Inc. April 2015	04/2015		D8	D8								E8		
D09	Goodman and Gilman's The Pharmacological Basis of Therapeutics, 10th ed / [edited by] Joel G. Hardman, Lee E. Limbird, Alfred Goodman Gilman, 2001, Chapter 1	2001	HBP4										E10		
D10	Rote Liste 2004, Clexane (Enoxaparin-Natrium)	2004	HBP5										E11		
D11	Kubitza et al., Pathophysiol. Haemost. Thromb. 2003, 33 (Suppl. 2), page 98, Abstract P0080	2003	HBP6				D4						E12		
D12	Kubitza et al., Pathophysiol. Haemost. Thromb. 2003, 33 (Suppl. 2), page 98, Abstract P0081	2003	HBP7										E13		
D13	Fareed et al., Clin Pharmacokinet 2003; 42 (12): 1043-1057	2003	HBP8					D5					E14		
D14	"Multiple Dose Regimene Malcolm Rowland, Thomas N. Tozer, in "Clinical pharmacokinetics concepts and application" 3rd edition, Lea and Felbiger, Philadelphia, 1995, pages 83 to 105	1995	HBP9					D7					E15		
D15	Harder et al., Pathophysiol. Haemost. Thromb. 2003; 33 (Suppl. 2), page 97, Abstract P0078	2003	HBP10				D5	D4		HW3			E16	D1	
D16	Perzborn et al., J. Thromb. Haemost. 2005 Mar; 3(3):514-21; published online on January 26, 2005	2005-01-26; 2005-01-24 (?)	HBP11			TM1					D4	D7	E17	D4	
D17	Confirmation of online publication date of HBP 11		HBP12										E18	D5	
D18	S. Harder et al.: "Effects of BAY 59-7939, an Oral Direct Factor Xa Inhibitor, on Thrombin Generation in Healthy Volunteers, Abstract# 3003 in: blood, vol. 103(11), 2003, page 811a	2003				TM2b					D8	D4			
D19	Ritschel, Bauer-Brandl: "Die Tablette", Editio Cantor Verlag, 2002, p. 1	2002				TM5									
D20	C. Kearon: "Duration of Venous Thromboembolism Prophylaxis After Surgery", Chest, 124, (6 Suppl.), Dec. 2003, p. 386S-392S	2003				TM6									
D21	Rowland, M., Tozer, T.: „Clinical Pharmacokinetics — Concepts and Applications", 3rd edition, 1995, p. 83 — 92, ISBN: 0-683-07404-0	1995					D6								
D22	Derendorf, H., Gramatté, T., Schäfer, H.: „Pharmakokinetik — Einführung in die Theorie und Relevanz für die Arznei-mitteltherapie, 2. Aufl., 2002, S. 16-67, ISBN:3-8047-1907-4	2002					D7								

Cross-reference table for consolidated document numbering in Oppositions against EP 1 845 961 B1

Consolidated Numbering	Reference	Publication Date	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13
D23	Weinz, C. et al.: „Metabolism and Distribution of [14C]BAY 59-7939 — an Oral, Direct Factor Xa Inhibitor — in Rat, Dog and Human", Drug Metabolism Reviews, 2004, 36 (suppl), p 98, abstract 196	2004					D8								
D24	Vrijens, B. et al.: „Non-vitamin K antagonist oral anticoagulants: considerations on once-vs. twice-daily regimens and their potential impact on medication adherence", Europace, 2015, 17, p. 514-523	2015					D9								
D25	Oberpichler-Schwenk, H.: "Rivaroxaban", Medizinische Monatsschrift für Pharmazeuten, 2008, 31(11), S. 412 bis 416	2008					D10								
D26	European Pharmacopeia, 5th edition, 15 June 2004, 2.9.3 Dissolution Test for Solid Dosage Forms	2004						D8							
D27	BIRKETT, D.J., "Pharmacokinetics made easy 11 Designing Dose Regimens", Aust Prescr, Vol 19, page 76-78, 1 July 1996	1996									D5				
D28	US 2007/0036065	2007									D6				
D29	ROEHRIG, S et al, "Discovery of the novel antithrombotic agent BAY 59-7939, an orally active, direct Factor Xa inhibitor", Abstract 156, Alfred Burger Award Symposium - Recent Advances towards Novel Cardiovascular Therapies, 228th ACS Meeting, Philadelphia, 22-26 August 2004	2004									D7	D8			
D30	Hospira UK Ltd and Genentech Inc, dated 10th April 2014, [2014] EWHC 1094 (Pat)	2014									D9				
D31	EU Clinical Trials Register, EudraCT Number 2004-002171-16 (Sweden), 17 November 2004	2004										D5			
D32	Malcolm Rowland, Thomas N. Tozer, in "Clinical Pharmacokinetics, concepts and applications", 3rd Edition, Lea and Febiger, Philadelphia 1995, p.1-7 (Why Clinical Pharmacokinetics?)	1995										D6			
D33	Patrono et al., Platelet Active Drugs, Chest 119,1, 39S-63S, 2001	2001											E19		
D34	Mueck et al., Clin. Pharmacokinet. 53,1-16, 2014	2014											E20		
D35	clinicaltrials.gov, Dose ranging study of Once Daily Regimen of BAY 59- 7939												E21		
D36	Charbonnier et al., Thromb. Haemost. 79(5), 897-901, 1998 (abstract from PubMed)	1998											E22		
D37	Turpie et al., BAY 59-7939 J.Thromb. Haemostat. 3, 2479-2486, 2005	2005											E23		
D38	Kubitza et al., Safety, Pharmacokinetics etc of BAY 59-7939. Clin. Pharm. Therapeutics, 78,4, 412-21, 2005	2005											E24		
D39	Griffin et al., The Textbook of Pharmaceutical Medicine, 4th ed., 2002	2002											E25		
D40	US Pharmacopeia USP 38 NF-33												E26		
D41	Harron, Dean W.G. et al., Bopindolol - A Review of its Pharacodynamic and Pharmacokinetic ..., Drugs, 41(0,130-149,1991	1991											E27		
D42	Clinical Pharmacology and Biopharmaceutics Review(s), CENTER FOR DRUG EVALUATION AND RESEARCH, Application No. 0224060rig1s000; 2009	2009											E28		

Cross-reference table for consolidated document numbering in Oppositions against EP 1 845 961 B1

Consolidated Numbering	Reference	Publication date	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13
D43	Cleveland Clinic Pharmacotherapy Update, "Enoxaparin Clinical Pearl", Vol. VI, No. 1, January/February 2003	2003												D2	
D44	Fareed et al., "Studies on the mechanism of action of BAY 59-7939 — an oral, direct Factor Xa inhibitor, Pathophysiol Haemost Thromb 2003; 33 (suppl2), PO 077													D3	
D45	Lieberman, A. et al.: "Pharmaceutical dosage forms"; Vol. 1-Tablets, p.172-181; Marcel Dekker 1980	1980													D3
D46	Sofia Mattsson: "Pharmaceutical Binders and Their Function in Directly Compressed Tablets — Mechanistic Studies on the Effect of Dry Binders on Mechanical Strength, Pore Structure and Disintegration of Tablets"; Comprehensive Summaries of Uppsala Dissertations from the Faculty of Pharmacy, 238, ACTA Universitatis Upsaliensis Uppsala 2000	2000													D4
D47	Rasenack N. et al., "Crystal habit and tableting behaviour; International Journal of Pharmaceutics 244 (2002), p. 45-57	2002													D5

Electronic Acknowledgement Receipt

EFS ID:	26556295
Application Number:	11883218
International Application Number:	
Confirmation Number:	9960
Title of Invention:	Prevention and Treatment of Thromboembolic Disorders
First Named Inventor/Applicant Name:	Frank Misselwitz
Customer Number:	21839
Filer:	Christine Hansen/Mich Sok
Filer Authorized By:	Christine Hansen
Attorney Docket Number:	11987-00042
Receipt Date:	05-AUG-2016
Filing Date:	16-JUL-2008
Time Stamp:	09:11:41
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$180
RAM confirmation Number	080516INTEFSW09130600
Deposit Account	024800
Authorized User	Mich Sok

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

37 CFR 1.17 (Patent application and reexamination processing fees)

37 CFR 1.19 (Document supply fees)

37 CFR 1.20 (Post Issuance fees)

37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	IDS_TL.pdf	7415998 ef29c71aeb8f888314803979956d45b9d16f8aaa	no	6
Warnings:					
Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	PTO_SB08.PDF	616183 f3ec9499c683e5272a09c3e954c440be1c362bdd	no	8
Warnings:					
A U.S. Patent Number Citation or a U.S. Publication Number Citation is required in the Information Disclosure Statement (IDS) form for autoloading of data into USPTO systems. You may remove the form to add the required data in order to correct the Informational Message if you are citing U.S. References. If you chose not to include U.S. References, the image of the form will be processed and be made available within the Image File Wrapper (IFW) system. However, no data will be extracted from this form. Any additional data such as Foreign Patent Documents or Non Patent Literature will be manually reviewed and keyed into USPTO systems.					
Information:					
3	Non Patent Literature	NPL1_20151230_Opposition_Substantiation_Henkel-Breuer_O01.pdf	3112352 1e63f1131820649031562cb4dd3f6479b05f12c3	no	25
Warnings:					
Information:					
4	Non Patent Literature	NPL2_20160106_Opposition_Actavis_O02.pdf	1356624 853469400e0159ffa4b37243e3fa59f94121587e	no	12
Warnings:					
Information:					
5	Non Patent Literature	NPL3_20160121_Opposition_Abdi-Ibrahim_O07.pdf	791944 7b870c8dda17c1920e0383d818b5543a31d2af43	no	9
Warnings:					
Information:					

6	Non Patent Literature	NPL4_20160121_Opposition_Generics_Ltd_O06.pdf	1193505 6005e685e9cfd0f18ac1e38712cdb0da1a831b3a	no	10
Warnings:					
Information:					
7	Non Patent Literature	NPL5_20160121_Opposition_Hamm-Wittkopp_O08.pdf	1589689 663a01d949a82b14177e75d8cd68b3d11ec30ef3	no	14
Warnings:					
Information:					
8	Non Patent Literature	NPL6_20160121_Opposition_Stada_O05.pdf	1900207 61c7e966f137f78c1bbac67b9c0e5b62afb623e5	no	27
Warnings:					
Information:					
9	Non Patent Literature	NPL7_20160121_Opposition_Teva_O04.pdf	2317692 051d0a6632dc24a3aa0da73dbd229560cd488078	no	14
Warnings:					
Information:					
10	Non Patent Literature	NPL8_20160121_Opposition_Zaklady_O03.pdf	1357184 dcf0090f1fd16c4c42b69becd643fb1c0371bcd4	no	12
Warnings:					
Information:					
11	Non Patent Literature	NPL9_20160122_Opposition_ABG-Patentes_O10.pdf	2729518 243ea2bc2998a5f4e0de963587baaa7948ebf19c	no	22
Warnings:					
Information:					
12	Non Patent Literature	NPL10_20160122_Opposition_Galenicum_Health_O09.pdf	3478479 7d67966635400e557de6771ff037d7d2b1e2f1f4	no	19
Warnings:					
Information:					

13	Non Patent Literature	NPL11_20160122_Opposition_Hexal_O12.pdf	1565224 a83897f076dbd16ef6126a12d26859762730d241	no	12
Warnings:					
Information:					
14	Non Patent Literature	NPL12_20160122_Opposition_Kraus-Weisert_O13.pdf	1353140 ca262515e02a019040f513b0b335ab1a7c3d8151	no	11
Warnings:					
Information:					
15	Non Patent Literature	NPL13_20160122_Opposition_Stolmar_O11.pdf	985624 53dbbb3147c201cef63607be7483b7a6a029ed7e	no	9
Warnings:					
Information:					
16	Non Patent Literature	NPL14_AULTON.pdf	943683 2a693799c7000715a892c5f6cef6f8c7900b8a5f	no	4
Warnings:					
Information:					
17	Non Patent Literature	NPL15_LIEBERMAN.pdf	603894 80aca18da9b44201265d5a86f25614bb6c286a1f	no	3
Warnings:					
Information:					
18	Non Patent Literature	NPL16_FOSTER.pdf	346600 73cc576b83bc48c955b31b6a28d145381c0fb997	no	3
Warnings:					
Information:					
19	Non Patent Literature	NPL17_Xarelto_Dosing_and_Transition_Management_Janssen.pdf	1175221 2df52b15bbde85fb54db321ef7421bb0b34e7b0e	no	3
Warnings:					
Information:					

20	Non Patent Literature	NPL18_GOODMAN.pdf	9177699 b48b18e4bcfe5c2bcd763c8265f04239e578a5f0	no	30
Warnings:					
Information:					
21	Non Patent Literature	NPL19_Rote_Liste_2004_Clexane.pdf	737387 594d000d7e0b0aa1060e33c2e5a6e4ed5fcc7b2e	no	3
Warnings:					
Information:					
22	Non Patent Literature	NPL20_KUBITZA.pdf	351299 037f8d1362ea64996ddef0a78aecb800d558ba5e	no	1
Warnings:					
Information:					
23	Non Patent Literature	NPL21_KUBITZA.pdf	351484 cceba98c186769036aa6c38ecdab5cabba6224c9	no	1
Warnings:					
Information:					
24	Non Patent Literature	NPL22_FAREED.pdf	3771391 1621f960e2c7da9b7f3b19066e483ecdd4517329	no	15
Warnings:					
Information:					
25	Non Patent Literature	NPL23_HARDER.pdf	370096 b97f7eb4781c47f44ecc20e41fd4f8332f9d5845	no	1
Warnings:					
Information:					
26	Non Patent Literature	NPL24_RITSCHEL.pdf	408998 61e942bcb057f4579c3f5c635c5219b5b0a5e296	no	3
Warnings:					
Information:					

27	Non Patent Literature	NPL25_KEARON.pdf	1831093 4fa524e79800bdfc40b0240919237ba292e6ae6e	no	7
Warnings:					
Information:					
28	Non Patent Literature	NPL26_DERENDORF.pdf	8690726 7985600b4e6d120be85eb3a49a08e81df6086657	no	23
Warnings:					
Information:					
29	Non Patent Literature	NPL27_WEINZ.pdf	1157213 0f682c146b971cc11dbc56457b88dfe6a6836d17	no	2
Warnings:					
Information:					
30	Non Patent Literature	NPL28_VRIJENS.pdf	2110898 527691183017caca850f7e3d25eafa2163e3312c	no	10
Warnings:					
Information:					
31	Non Patent Literature	NPL29_OBERPICHLER-SCHWENK.pdf	1341809 8619babd378325f29c93e205f495f5f74df526ce	no	5
Warnings:					
Information:					
32	Non Patent Literature	NPL30_European_Pharmacopeia.pdf	1174149 c8091d3f72185fda9cb481f52ca1442edd13264b	no	4
Warnings:					
Information:					
33	Non Patent Literature	NPL31_BIRKETT.pdf	682326 648532e4ab77fa7ae875b6c038d92cf8d03ccb1e	no	6
Warnings:					
Information:					

34	Non Patent Literature	NPL32_Hospira_Genentech.pdf	7440283 c32ad09f572d1370f0be873a18ca82b287a54bad	no	47
Warnings:					
Information:					
35	Non Patent Literature	NPL33_EU_Clinical_Trials.pdf	642202 8bf6833477260d9161b86870708b7a449513a70a	no	5
Warnings:					
Information:					
36	Non Patent Literature	NPL34_ROWLAND.pdf	1188754 4fae94d178f9b457c6a825a46b852c6ae261b799	no	7
Warnings:					
Information:					
37	Non Patent Literature	NPL35_PATRONO.pdf	6730746 398e74e040ff7064d107ef8047adf9c1f483e328	no	25
Warnings:					
Information:					
38	Non Patent Literature	NPL36_MUECK.pdf	3523653 26718c4782a3cb7168b98b443522ee84e978597a	no	16
Warnings:					
Information:					
39	Non Patent Literature	NPL37_ClinicalTrials.pdf	382939 b395dc0ea780d25b1b52a66316c68998205fd202	no	3
Warnings:					
Information:					
40	Non Patent Literature	NPL38_CHARBONNIER.pdf	132754 e89e133abac83eadf262a19ca9793dd758caed23	no	1
Warnings:					
Information:					

41	Non Patent Literature	NPL39_TURPIE.pdf	1668154 d89b8a902f0332771c40c4025d07c932f113a12f	no	8
Warnings:					
Information:					
42	Non Patent Literature	NPL40_KUBITZA.pdf	1787447 644abeac588d1bf86885c9a21b06f18de1291d80	no	10
Warnings:					
Information:					
43	Non Patent Literature	NPL41_GRIFFIN.pdf	611379 5b2f13641cedf6fddf9dffb6449b4d40375e4b5a	no	6
Warnings:					
Information:					
44	Non Patent Literature	NPL42_US_Pharmacopeia.pdf	4371380 3eb573b4ccfb1e3dee1d99de891d966bb91bb0b9	no	17
Warnings:					
Information:					
45	Non Patent Literature	NPL43_HARRON.pdf	5989726 cf0580e978303c30a39abe48bbdc404e78cd6c6d	no	20
Warnings:					
Information:					
46	Non Patent Literature	NPL44_Clinical_Pharmacology_Biopharmaceutics_Reviews_part_1.pdf	16544951 7e1e9484a6dccc80def7f0af811d72220ddd5c51	no	139
Warnings:					
Information:					
47	Non Patent Literature	NPL45_Cleveland_Clinic_Pharmacotherapy_Update.pdf	340371 72647dce41967b85705888fe1598dc2adc0b5d7b	no	2
Warnings:					
Information:					

48	Non Patent Literature	NPL46_FAREED.pdf	331746 69f6fe806793bb9992bb90966dac7935274b1178	no	1
Warnings:					
Information:					
49	Non Patent Literature	NPL47_LIEBERMAN.pdf	2761933 43cebfe0fe278d15bea7868c757a17032efbc5b7	no	7
Warnings:					
Information:					
50	Non Patent Literature	NPL48_MATTSSON.pdf	10521212 a2b3594986563f4c0475792b3354b8df072e24dc	no	62
Warnings:					
Information:					
51	Non Patent Literature	NPL49_RASENACK.pdf	2732950 872002d2188e3e66c1cddddc6200d7c33274edfb	no	13
Warnings:					
Information:					
52	Fee Worksheet (SB06)	fee-info.pdf	30305 99fc049e486119bc4ea8b32bdd67987770fbc138	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	134722214	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/883,218	07/16/2008	Frank Misselwitz	11987-00042	9960

21839 7590 06/03/2016

BUCHANAN, INGERSOLL & ROONEY PC
POST OFFICE BOX 1404
ALEXANDRIA, VA 22313-1404

EXAMINER
KAROL, JODY LYNN

ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
06/03/2016	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ADIPDOC1@BIPC.com

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte FRANK MISSELWITZ, DAGMAR KUBITZA, SON-MI PARK, and KLAUS WEHLING

Appeal 2014-004087
Application 11/883,218[1]
Technology Center 1600

Before ERIC B. GRIMES, JOHN G. NEW, and RYAN H. FLAX, *Administrative Patent Judges*.

FLAX, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134(a) involving claims directed to a method of treating a thromboembolic disorder with rivaroxaban administered once daily, for five consecutive days, via a rapid-release oral dosage. Claims 1, 4, 5, 11, and 18 are on appeal as rejected under the doctrine of non-statutory obviousness type double patenting and 35 U.S.C. § 103(a). We have jurisdiction under 35 U.S.C. § 6(b).

We affirm-in-part.

---

[1] The Real Party in Interest is Bayer Pharma Aktiengesellschaft of Berlin, Germany. App. Br. 1.

STATEMENT OF THE CASE

The appealed claims can be found in the Claims Appendix of the Appeal Brief. Claim 1 is the sole independent claim and reads as follows:

> 1. A method of treating a thromboembolic disorder comprising administering a direct factor Xa inhibitor that is 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide no more than once daily for at least five consecutive days in a rapid-release oral dosage form to a patient in need thereof.

App. Br. 12 (Claims Appendix).

The following grounds of rejection are on appeal:

A. Claims 1, 4, 5, 11, and 18 rejected under the doctrine of nonstatutory obviousness-type double patenting over claims 13, 24, and 30 of Straub 456[2] in view of Kubitza 1[3] and Kubitza 2.[4] Final Action 9.

B. Claims 1, 4, 5, 11, and 18 rejected under the doctrine of nonstatutory obviousness-type double patenting over claims 1–6 and 17–21 of Straub 339[5] in view of Kubitza 1 and Kubitza 2. Final Action 11.

---

[2] U.S. Patent US 7,157,456 B2 (issued Jan. 2, 2007) (hereinafter "Straub 456").
[3] Kubitza et al., *Oral, Direct Factor Xa Inhibitor – In Healthy Male Subjects*, 102 BLOOD 811a (Nov. 16, 2003) (hereinafter "Kubitza 1").
[4] Kubitza et al., *Single Dose Escalation Study Investigating the Pharmacodynamics, Safety, and Pharmacokinetics of BAY 59-7939 and Oral, Direct Factor Xa Inhibitor in Healthy Male Subjects*, 102 BLOOD 813a, Abstract (Nov. 16, 2003) (hereinafter "Kubitza 2").
[5] U.S. Patent US 7,592,339 B2 (issued Sept. 22, 2009) (hereinafter "Straub 339").

C. Claims 1, 4, 5, 11, and 18 rejected under 35 U.S.C. § 103(a) over Straub 610,[6] Kubitza 1, and Kubitza 2. Final Action 14.

FINDINGS OF FACT

FF1. The recited "5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide" is called rivaroxaban by those of ordinary skill in the art (hereinafter, we refer to this as "rivaroxaban"). Final Action, e.g., 5; App. Br., e.g., 3.

FF2. The Specification defines "treatment" as "includ[ing] the therapeutic and/or prophylactic treatment of thromboembolic disorders." Spec. 9, ll. 1–2.

FF3. The Specification defines "oral dosage forms" as "pharmaceutical products administered orally . . . recognized by those skilled in the art to include such forms as liquid formulations, granules, gelcaps, hard gelatine capsules or sachets filled with granules, and tablets releasing the active compound rapidly or in a modified manner." Spec. 10, ll. 3–6.

FF4. The Specification defines "rapid-release tablets" as "those which, according to the USP release method using apparatus 2 (paddle), have a Q value (30 minutes) of 75 %." Spec. 10, ll. 7–9.

FF5. The Specification defines "once daily" as "administration of the drug once a day and includes the administration of one dosage form as well

[6] U.S. Patent Application Pub. US 2003/0153610 A1 (published Aug. 14, 2003) (hereinafter "Straub 610"). Straub 610 issued as Straub 456.

as administration of two or more dosage forms simultaneously or consecutively within a short time period." Spec. 10, ll. 18–20.

FF6. Straub 456 recited at claim 13 "treatment of a thromboembolic disorder comprising administering to a patient in need thereof an effective amount of a compound of claim 1 [undisputed to comprise rivaroxaban] wherein the thromboembolic disorder is myocardial infarct, pulmonary embolism or deep venous thrombosis." Straub 456 claims 1 and 13; *see also* Final Action 9–10 (discussing Straub 456).

FF7. Straub 339 recited at claim 1 "[a] method for inhibiting thrombus formation comprising administering an effective amount of [rivaroxaban; *see* App. Br. 3, n.2] or a hydrate thereof, to a patient in need of said method." Straub 339 claim 1; *see also* Final Action 11–12 (discussing Straub 339).

FF8. Kubitza 1 disclosed administration of BAY 59-7939 [rivaroxaban; App. Br. 5] to "healthy male subjects" as a 5 mg once daily ("od"), oral dose on "Day 0" and on "Days 4-8." Kubitza left col., first through fourth paragraphs; *see also* Final Action 10–13, 16–17 (discussing Kubitza 1).

FF9. Kubitza 1 disclosed "BAY 59-7939 was safe and well tolerated after multiple-dose administration at all the doses tested, with no signs of bleeding. BAY 59-7939 inhibited FXa [factor Xa] activity . . . ." Kubitza 1 right col., last section (Conclusions).

FF10. Kubitza 2 disclosed administering BAY 59-7939 to "103 healthy men" as either 1.25–80 mg tablet (under fasting conditions) or a 5–

10 mg dose as oral solution. Kubitza 2 (Abstract); *see also* Final Action 10–13, 16–17 (discussing Kubitza 2).

FF11. Kubitza 2 disclosed "BAY 59-7939 showed a rapid onset of action with maximal effects being observed after 2 hours" and "[a]fter administration of the oral solution, maximal plasma concentrations were observed after about 0.5 hours . . ." and "[l]ower peak concentrations of approximately 50% were observed 2 hours after administration of the tablet." Kubitza 2 (Abstract); *see also* Final Action 10–13, 16–17 (discussing Kubitza 2).

FF12. Kubitza 2 disclosed "BAY 59-7939 offers predictable anticoagulation with an excellent safety profile." Kubitza 2 (Abstract).

FF13. Straub 610 disclosed compounds to treat or prevent thromboembolic disorders. Straub 610 ¶¶ 9–18; *see also* Final Action 15 (discussing Straub 610). Straub 610 disclosed that rivaroxaban is particularly preferred. Straub 610 ¶¶ 145, 617–635 (Example 44). Straub 610 disclosed that oral administration is preferred and states that suitable formulations include tablets and solutions. Straub 610 ¶¶ 366–367.

DISCUSSION

We address both obviousness-type double patenting rejections and the § 103(a) rejection together because they hinge on the same facts and arguments.

The Examiner determined that the claims of Straub 456 and Straub 339 are directed to administering rivaroxaban to a patient in need of thromboembolic disorder treatment and that Kubitza 1 and Kubitza 2 would have made it obvious to administer rivaroxaban in the claimed methods, that

is, once daily, for at least five consecutive days, in a rapid-release oral dosage form. Final Action 10–13; *see also* FF6–FF12 (identifying the teachings of the references).

We agree with the Examiner's determination. Specifically, Kubitza 1 disclosed oral administration of rivaroxaban once daily for five consecutive days (FF8) was safe and well tolerated (FF9). Kubitza 2 disclosed administration of rivaroxaban as an oral solution (FF10) produced maximal plasma concentrations after 0.5 hours (FF11) and showed an excellent safety profile (FF12). Based on these teachings, it would have been obvious to practice the methods claimed by Straub 456 and Straub 339 by administering rivaroxaban once daily, for at least five consecutive days, as an oral solution. The Specification lists a variety of oral dosages, e.g., liquids and tablets. *See* FF3. We find that the oral solution disclosed by Kubitza 2 is a rapid release oral dosage form as recited by appealed claim 1 because an oral solution is an oral dosage form, which would rapidly release.

The Examiner determined that Straub 610 disclosed oral administration of rivaroxaban to patients (in need thereof) to treat or prevent thromboembolic disorders. Final Action 15; *see also* FF13 (indicating Straub 610's relevant disclosure). The Examiner determined that Kubitza 1 disclosed administering rivaroxaban to patients as an oral dosage for five consecutive days (as a factor Xa inhibitor). Final Action 16; *see also* FF8–FF9 (identifying Kubitza 1's disclosure). The Examiner determined that Kubitza 2 disclosed administering rivaroxaban to patients as a rapid release oral dosage. Final Action 16; *see also* FF10–FF12 (identifying Kubitza 2's disclosure). The Examiner determined that a person of ordinary skill in the

art would have been motivated to combine Kubitza 1 and Kubitza 2 with Straub 610 for their teachings how to effectively and safely administer the same drug of Straub 610 for the same purpose of Straub 610 (that is, to inhibit Factor Xa and treat a thromboembolic disorder, such as deep vein thrombosis). Final Action 16–17. These determinations by the Examiner set forth a prima facie case of obviousness for independent claim 1.

Appellants argue that Kubitza 1 and Kubitza 2 are "irrelevant to the presently claimed invention because they merely report studies of the 'pharmacodynamics, safety, and pharmacokinetics' of rivaroxaban in 'healthy male subjects.'" App. Br. 5, 10. Appellants argue that because these are not "patients in need of treatment for or at a significantly increased risk for thromboembolic disorders," their teachings are inapplicable. *Id.* We are not persuaded by these arguments.

The Straub 456 and Straub 339 patents claim, and Straub 610 disclosed, the treatment of a thromboembolic disorder (e.g., inhibiting thrombus in patients that need such treatment) by administering rivaroxaban. *See* FF6–FF7, FF13. Having this information in hand, a person of ordinary skill in the art would reasonably look to and combine with any of these references the disclosures of Kubitza 1 and Kubitza 2, which teach how one can safely administer the drug rivaroxaban. *See* FF8 and FF10. Whether Kubitza 1 and Kubitza 2 are directed to healthy or ill individuals is not significant because Appellants' Specification defines "treatment" as including "prophylactic treatment" (FF2), i.e., administration to healthy people to prevent thromboembolic disorders from developing. Moreover,

the Straub references are each directed to treating ill individuals. FF6, FF7, FF13.

For these reasons, the Examiner's rejections of claim 1 over Straub 456, Straub 339, and/or Straub 610 in view of Kubitza 1 and Kubitza 2 are affirmed. Claims 4, 11, and 18 fall with claim 1 because they were not argued separately. 37 C.F.R. § 41.37(c)(1)(iv).

With respect to claim 5, Appellants identify that "[t]he Examiner acknowledges that Straub does not teach . . . 'a rapid release tablet as claimed in the instant claim 5.'" App. Br. 9.

The Examiner conceded that the Straub 456, Straub 339, and Straub 610 references did not claim or disclose the "rapid release" tablet of claim 5. Final Action 10, 12, 15–16. For this, the Examiner relied on Kubitza 2, which disclosed "BAY 59-7939 showed a rapid onset of action with maximal effects being observed after 2 hours" and "peak concentrations of approximately 50% were observed 2 hours after administration of the tablet." Kubitza 2 (Abstract); *see also* FF11; Final Action 16 and Ans. 13 (discussing Kubitza 2).

Appealed claim 5 recites a "*rapid-release tablet*," which we interpret in view of the express definition thereof provided in the Specification, which is "those [tablets] which, according to the USP release method using apparatus 2 (paddle), have a Q value (30 minutes) of 75 %." FF4. The only disclosure of Kubitza 2 directed to drug release by tablets is that "[l]ower peak concentrations of approximately 50% were observed 2 hours after administration of the tablet." Kubitza 2 (Abstract). Based on the evidence of record we cannot conclude that this disclosure indicates a "rapid-release

tablet" as defined in the Specification. Moreover, the Examiner has offered no explanation as to how the disclosure of Kubitza 2 teaches or suggest a rapid-release tablet in line with the interpretation of this claim language. Therefore, we find Appellants' argument (*see* App. Br. 9) concerning the patentability of claim 5 over the combined references persuasive and reverse the Examiner's rejections of claim 5 over Straub 456, Straub 339, or Straub 610 in view of or combined with Kubitza 1 and Kubitza 2.

SUMMARY

The rejection of claims 1, 4, 5, 11, and 18 under the doctrine of nonstatutory obviousness-type double patenting over claims 13, 24, and 30 of Straub 456 in view of Kubitza 1 and Kubitza 2 is affirmed as to claims 1, 4, 11, and 18, and reversed as to claim 5.

The rejection of claims 1, 4, 5, 11, and 18 under the doctrine of nonstatutory obviousness-type double patenting over claims 1–6 and 17–21 of Straub 339 in view of Kubitza 1 and Kubitza 2 is affirmed as to claims 1, 4, 11, and 18, and reversed as to claim 5.

The rejection of claims 1, 4, 5, 11, and 18 under 35 U.S.C. § 103(a) over Straub 610, Kubitza 1, and Kubitza 2 is affirmed as to claims 1, 4, 11, and 18, and reversed as to claim 5.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED-IN-PART

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/883,218	07/16/2008	Frank Misselwitz	11987-00042	9960

21839 7590 03/24/2014

BUCHANAN, INGERSOLL & ROONEY PC
POST OFFICE BOX 1404
ALEXANDRIA, VA 22313-1404

EXAMINER	
KAROL, JODY LYNN	

ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
03/24/2014	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ADIPDOC1@BIPC.com

United States Patent and Trademark Office

Under Secretary of Commerce for Intellectual Property and
Director of the United States Patent and Trademark Office
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

BUCHANAN, INGERSOLL & ROONEY PC
POST OFFICE BOX 1404
ALEXANDRIA, VA 22313-1404

Appeal No: 2014-004087

Application: 11/883,218

Appellant: Frank Misselwitz et al.

Patent Trial and Appeal Board Docketing Notice

Application 11/883,218 was received from the Technology Center at the Board on January 30, 2014 and has been assigned Appeal No: 2014-004087.

In all future communications regarding this appeal, please include both the application number and the appeal number.

The mailing address for the Board is:

PATENT TRIAL and APPEAL BOARD
UNITED STATES PATENT AND TRADEMARK OFFICE
P.O. BOX 1450
ALEXANDRIA, VIRGINIA 22313-1450

Telephone inquiries can be made by calling 571-272-9797 and referencing the appeal number listed above.

By order of the Patent Trial and Appeal Board.

SS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of Misselwitz, Frank et al. Application No.: 11/883,218 Filed: July 16, 2008 For: Prevention and Treatment of Thromboembolic Disorders	Confirmation No.: 9960 Group Art Unit: 1627 Examiner: Karol, Jody Lynn

REPLY BRIEF PURSUANT TO 37 CFR §41.41

MS Appeal Brief- Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Madam:

Appellants hereby file this Reply Brief in response to the Examiner's Answer mailed November 22, 2013.

I. REAL PARTY IN INTEREST

The Appeal Brief filed on April 20, 2012 identified the real party in interest as Bayer Pharma Aktiengesellschaft of Berlin, Germany. Bayer Pharma Aktiengesellschaft has since recorded an assignment of its rights to Bayer Intellectual Property GmbH of Monheim, Germany. The real party in interest is Bayer Intellectual Property GmbH.

II. ONCE DAILY ADMINISTRATION SURPRISINGLY WAS AS EFFECTIVE AS TWICE DAILY ADMINISTRATION.

The claims at issue concern dosaging of one drug: 5-chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide, also known as rivaroxaban.

The Patent Office asserts in their Answer that Kubitza[1] and Kubitza[2] teach once daily dosing of rivaroxaban in rapid release tablets, which would be preferred where patient compliance is an issue.

Answer, p. 13. However, as Applicants stated previously, Kubitza[1] and Kubitza[2] involve administration of rivaroxaban to ***healthy*** people. In contrast, Applicants' claim methods of treating ***ill*** patients. The Patent Office has failed to address the surprising results Applicants report in the specification for once daily dosaging of ill people.

Applicants studied dosaging in patients undergoing hip replacement surgery and therefore at risk of thromboembolism during surgery and recovery. Surprisingly, Applicants found that once daily dosaging was as effective as twice daily dosaging. Page 3, lines 15-18. In summarizing the results of the clinical studies, Applicants state in the specification: "On the basis of total daily doses the 30 mg once daily dose fits very well into the dose dependence observed in the range of 2.5 to 30 mg bid [twice daily] which corresponds to total daily doses of 5 to 60 mg." Page 12, lines 25-26. The data in table 1-1 shows that the results for efficacy in hip replacement patients for 30 mg od (once daily) fall between 20 mg and 40 mg total dosages, each of which were administered bid (twice daily). Thus, the data in table 1-1 shows efficacy of once daily dosaging fell where one would have expected a twice daily dosage to be. From this, the inventors concluded that once daily dosaging of rivaroxaban with a rapid release formulation to treat thromboembolism was possible. Even assuming arguendo that the Patent Office had presented a *prima facie* case of obviousness (which we do not agree), this rebuttal evidence in the specification shows the surprising result that once a day dosaging can be as effective as twice daily dosaging.

III. THE TOTALITY OF THE ART SHOWS THE CLAIMED METHOD IS CONTRARY TO ACCEPTED WISDOM AND THEREFORE NONOBVIOUS.

Furthermore, "[t]he totality of the prior art must be considered, and proceeding contrary to accepted wisdom in the art is evidence of nonobviousness." MPEP 2145, citing *In re Hedges,* 783 F.2d 1038 (Fed. Cir. 1986). Rowland and Tozer shows that dosing every half-life is desirable. *See* Rowland and Tozer, "Clinical Pharmacokinetics Concepts and Applications, Third Ed.," Williams & Wilkins (1985), at p. 83, cited in specification at page 3, lines 7-9 and in IDS submitted June 5, 2009. When Kubitza[1] and Kubitza[2] are considered in view of the totality of the prior art, one sees that the pharmaceutical scientist of ordinary skill in the art would ***not*** have been motivated to administer rivaroxaban once daily when it was reported to have a half-life of 3-4 hours (Kubitza[2]) or 4-6 hours (Kubitza[1]).

The Patent Office responds that Kubitza[1] and Kubitza[2] teach once daily dosing. Answer, page 13. However, this is used in studies in healthy patients to examine the pharmacodynamics, safety and pharmacokinetics of rivaroxaban, not to measure its efficacy. In contrast, the present claims are to methods of ***effective treatment*** of a thromboembolic disorder. Kubitza[1] and Kubitza[2] do not teach effective dosages; they show safe dosages. The scientist of ordinary skill in pharmaceutical dosaging looks to factors beyond initial safety tests to determine efficacious dosages, such as to half-life. The Patent Office has not addressed the totality of the art. The Patent Office should not establish a precedent that safety studies in healthy volunteers renders obvious dosage regimens contrary to commonly accepted wisdom for efficacious treatment of patients suffering from a disease.

IV. CONCLUSION

In sum, for the reasons of record and the reasons discussed above, reversal of the obviousness-type double patenting and obviousness rejections and allowance of the claims is respectfully requested.

No fees are believed to be required for the filing of this Reply Brief. However, if a fee is due, the Commissioner is hereby authorized to charge any appropriate fees under 37 C.F.R. §§1.16, 1.17, and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 02-4800.

Respectfully submitted,

Date: January 21, 2014

Christine M. Hansen

Christine M. Hansen
Registration No.: 40,634
BUCHANAN INGERSOLL & ROONEY PC
1005 North Market Street, Ste. 1900
Wilmington, Delaware 19801
(302) 552-4249
(302) 552-4295 (Fax)
Attorney for Applicant

Customer No. 21839

Electronic Acknowledgement Receipt

EFS ID:	17963642
Application Number:	11883218
International Application Number:	
Confirmation Number:	9960
Title of Invention:	Prevention and Treatment of Thromboembolic Disorders
First Named Inventor/Applicant Name:	Frank Misselwitz
Customer Number:	21839
Filer:	Christine Hansen/Melissa Seebaran
Filer Authorized By:	Christine Hansen
Attorney Docket Number:	11987-00042
Receipt Date:	21-JAN-2014
Filing Date:	16-JUL-2008
Time Stamp:	11:57:33
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Reply Brief Filed	Reply_Brief.pdf	325933 44b2ebad9a190a26fbc3aec1610a4332c923817b	no	3

Warnings:	
Information:	

Total Files Size (in bytes):	325933

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/883,218	07/16/2008	Frank Misselwitz	11987-00042	9960

21839 7590 11/22/2013

BUCHANAN, INGERSOLL & ROONEY PC
POST OFFICE BOX 1404
ALEXANDRIA, VA 22313-1404

EXAMINER	
KAROL, JODY LYNN	
ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
11/22/2013	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ADIPDOC1@BIPC.com

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Application Number: 11/883,218
Filing Date: 7/16/2008
Appellant(s): Misselwitz et al.

Christine M. Hansen
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 4/20/212.

(1) Grounds of Rejection to be Reviewed on Appeal

The ground(s) of rejection set forth in the Office action dated 9/21/2011 from which the appeal is taken have been modified in view of the amendment filed on 1/30/2012 and upon further consideration. A list of rejections withdrawn by the examiner (if any) is included under the subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

The following ground(s) of rejection are applicable to the appealed claims.

Double Patenting

Nonstatutory Double Patenting

1. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

2. Claims 1, 4, 5, 11, and 18 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 13, 24, and 30 of U.S. Patent No. 7,157,456 B2 in view of Kubitza et al.[1] ("Multiple dose escalation study investigating the pharmacodynamics, safety, and pharmacokinetics of BAY 59-7939 an oral, direct Factor Xa inhibitor in healthy male subjects," *Blood*, Vol. 102:11 16 Nov. 2003, pgs 811a - cited on IDS) and Kubitza et al.[2] (ABSTRACT 3010, "Single Dose escalation study investigating the pharmacodynamics, safety, and pharmacokinetics of BAY 59-7939 an oral, direct Factor Xa inhibitor in healthy male subjects," *Blood*, Vol. 102:11, 16 Nov. 2003, page 813a - cited on IDS).

Although the conflicting claims are not identical, they are not patentably distinct from each other because they are both directed to methods of treating thromboembolic disorders comprising administering 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-mopholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide (rivaroxaban).

The patented claims do not teach administering 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-mopholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide (rivaroxaban) once daily for at least five consecutive days. The patented claims do not teach the plasma concentration half-life in a human patient or that the dosage form is a rapid release.

Kubitza et al.[1] teach administering 5 mg of BAY 59-7939 (rivaroxaban) once daily to male subjects on day 0 and days 4-8 (i.e. five consecutive days) (see page 811a, subjects and methods).

Kubitza et al.[2] teach administering 1.25 mg to 80 mg of BAY 59-7939 (rivaroxaban) under fasting conditions as a tablet to men, wherein BAY 59-7939 showed rapid onset of action (i.e. rapid release). Kubitza et al. also teach the plasma concentration half-life of the tablet containing BAY 59-7939 was observed 2 hours after administration. Kubitza et al. further teach BAY 59-7939 is safe and well-tolerated across a wide range of oral doses (1.25 mg to 80 mg) (see abstract# 3010).

It would have been obvious to one of ordinary skill in the art at the time of the invention to treat deep venous thromboses in a patient by administering rivaroxaban as disclosed by the patented claims using the administration guidelines and tablets taught by Kubitza et al.[1] and Kubitza et al.[2] One of ordinary skill in the art would have been motivated to administer rivaroxaban for 5 consecutive days as taught by Kubitza et al.[1] in order to effectively treat deep vein thromboses. One of ordinary skill in the art would have been motivated to administer rivaroxaban once daily using the rapid release tablet Kubitza et al.[2] in order to provide patient convenience and compliance. One of ordinary skill in the art would have had a reasonable expectation of success in treating deep venous thromboses in a patient by administering rivaroxaban as disclosed by the patented claims using the administration guidelines and tablets taught by Kubitza et al.[1] and Kubitza et al.[2] because rivaroxaban is known to treat deep venous thromboses, and

Kubitza et al.[1] and Kubitza et al.[2] teach administration guidelines for rivaroxaban that are safe and tolerable for patients.

3. Claims 1, 4, 5, 11, and 18 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6 and 17-21 of U.S. Patent No. 7,592,339 B2 in view of Kubitza et al.[1] ("Multiple dose escalation study investigating the pharmacodynamics, safety, and pharmacokinetics of BAY 59-7939 an oral, direct Factor Xa inhibitor in healthy male subjects," *Blood*, Vol. 102:11 16 Nov. 2003, pgs 811a - cited on IDS) and Kubitza et al.[2] (ABSTRACT 2010, "Single Dose escalation study investigating the pharmacodynamics, safety, and pharmacokinetics of BAY 59-7939 an oral, direct Factor Xa inhibitor in healthy male subjects," *Blood*, Vol. 102:11, 16 Nov. 2003, page 813a - cited on IDS).

Although the conflicting claims are not identical, they are not patentably distinct from each other because they are both directed to methods of treating thromboembolic disorders comprising administering 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-mopholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide (rivaroxaban)..

The patented claims do not teach administering 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-mopholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide (rivaroxaban) once daily for at least five consecutive days. The patented claims do not teach the plasma concentration half-life in a human patient. The patented claims do not teach a rapid release tablet as claimed in the instant claims 5, 10, 11, and 14.

Kubitza et al.[1] teach administering 5 mg of BAY 59-7939 (rivaroxaban) once daily to male subjects on day 0 and days 4-8 (i.e. five consecutive days) (see page 811a, subjects and methods).

Kubitza et al.[2] teach administering 1.25 mg to 80 mg of BAY 59-7939 (rivaroxaban) under fasting conditions as a tablet to men, wherein BAY 59-7939 showed rapid onset of action (i.e. rapid release). Kubitza et al. also teach the plasma concentration half-life of the tablet containing BAY 59-7939 was observed 2 hours after administration. Kubitza et al. further teach BAY 59-7939 is safe and well-tolerated across a wide range of oral doses (1.25 mg to 80 mg) (see abstract# 3010).

It would have been obvious to one of ordinary skill in the art at the time of the invention to treat deep venous thromboses in a patient by administering rivaroxaban as disclosed by the patented claims using the administration guidelines and tablets taught by Kubitza et al.[1] and Kubitza et al.[2] One of ordinary skill in the art would have been motivated to administer rivaroxaban for 5 consecutive days as taught by Kubitza et al.[1] in order to effectively treat deep vein thromboses. One of ordinary skill in the art would have been motivated to administer rivaroxaban once daily using the rapid release tablet Kubitza et al.[2] in order to provide patient convenience and compliance. One of ordinary skill in the art would have had a reasonable expectation of success in treating deep venous thromboses in a patient by administering rivaroxaban as disclosed by the patented claims using the administration guidelines and tablets taught by Kubitza et al.[1] and Kubitza et al.[2] because rivaroxaban is known to treat deep venous thromboses, and

Kubitza et al.[1] and Kubitza et al.[2] teach administration guidelines for rivaroxaban that are safe and tolerable for patients.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1, 4, 5, 11, and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Straub et al. (US 2003/0156310 A1) in view of Kubitza et al.[1] ("Multiple dose escalation study investigating the pharmacodynamics, safety, and pharmacokinetics of BAY 59-7939 an oral, direct Factor Xa inhibitor in healthy male subjects," *Blood*, Vol. 102:11 16 Nov. 2003, pgs 811a - cited on IDS) and Kubitza et al.[2] (ABSTRACT 3010, "Single Dose escalation study investigating the pharmacodynamics, safety, and pharmacokinetics of BAY 59-7939 an oral, direct Factor Xa inhibitor in healthy male subjects," *Blood*, Vol. 102:11, 16 Nov. 2003, page 813a - cited on IDS).

The instant claims are directed to methods of treating deep vein thromboses comprising administering 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-mopholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide (rivaroxaban) no more than once daily for at least five consecutive days in a rapid-release oral dosage form to a patient in need thereof, wherein said inhibitor has a plasma concentration half-life of 10 hours or less when orally administered to a human patient.

Straub et al. teach oxazolidinone derivatives for the treatment of thromboembolic disorders including deep venous thromboses (see abstract; pages 1-2, sections [009]--[0010]; page 17, sections [0392]-[0393]; page 74, claim 10). Straub et al. teach 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-mopholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide (rivaroxaban) as preferred compound (see page 6, section [0145]; page 26, Example 44). Straub et al. teach oral administration is preferred,

wherein oral formulations include tablets as claimed in the instant claim 5 (see page 15, sections [0366]-[0367]).

Straub et al. do not teach administering 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-mopholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide (rivaroxaban) once daily for at least five consecutive days. Straub et al. do not teach the plasma concentration half-life in a human patient. Straub et al. do not teach a rapid release tablet as claimed in the instant claim 5.

Kubitza et al.[1] teach administering 5 mg of BAY 59-7939 (rivaroxaban) once daily to male subjects on day 0 and days 4-8 (i.e. five consecutive days) (see page 811a, subjects and methods).

Kubitza et al.[2] teach administering 1.25 mg to 80 mg of BAY 59-7939 (rivaroxaban) under fasting conditions as a tablet to men, wherein BAY 59-7939 showed rapid onset of action (i.e. rapid release). Kubitza et al. also teach the plasma concentration half-life of the tablet containing BAY 59-7939 was observed 2 hours after administration. Kubitza et al. further teach BAY 59-7939 is safe and well-tolerated across a wide range of oral doses (1.25 mg to 80 mg) (see abstract# 3010).

It would have been obvious to one of ordinary skill in the art at the time of the invention to treat deep venous thromboses in a patient by administering rivaroxaban as taught by Straub et al. using the administration guidelines and tablets taught by Kubitza et al.[1] and Kubitza et al.[2] One of ordinary skill in the art would have been motivated to administer rivaroxaban for 5 consecutive days as taught by Kubitza et al.[1] in order to effectively treat deep vein thromboses. One of ordinary skill in the art would have been

motivated to administer rivaroxaban once daily using the rapid release tablet Kubitza et al.[2] in order to provide patient convenience and compliance. One of ordinary skill in the art would have had a reasonable expectation of success in treating deep venous thromboses in a patient by administering rivaroxaban as taught by Straub et al. using the administration guidelines and tablets taught by Kubitza et al.[1] and Kubitza et al.[2] because rivaroxaban is known to treat deep venous thromboses, and Kubitza et al.[1] and Kubitza et al.[2] teach administration guidelines for rivaroxaban that are safe and tolerable for patients.

Thus, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art.

WITHDRAWN REJECTIONS

The following grounds of rejection are not presented for review on appeal because they have been withdrawn by the examiner.

Upon further consideration, the rejection of claims 1, 4, 5, 11, and 18 as being directed to an invention not patentably distinct from claims 13, 24, and 30 of commonly assigned US 7,157,456 B2 I herein withdrawn.

Upon further consideration, the rejection of claims 1, 4, 5, 11, and 18 as being directed to an invention not patentably distinct from claims 1-6 and 17-21 of commonly assigned US 7,592,399 B2 is herein withdrawn.

In view of the amendment filed on 1/30/2012, amending claims 1 and 5, the rejection of claims 1, 4, 5, 11, and 18 under 35 U.S.C. 112, second paragraph, as being indefinite, is herein withdrawn.

(2) Response to Argument

A. In response to Appellant's arguments that claims 1, 4, 5, 11, and 18 are patentably distinct from claims 13, 24, and 30 of US Patent No. 7,157,456 and claims 1-6 and 17-21 of US Patent No. 7,592,339, it is noted that said rejections have been herein withdrawn.

B. Appellant argues with regard to the rejection of claims 1, 4, 5, 11, and 18 on the ground of nonstatutory obviousness-type double patenting based on claims 13, 24, and 30 of US Patent No. 7,157,456 or claims 1-6 and 17-21 of US Patent No. 7,592,339 in view of Kubitza[1] and Kubitza[2] that Kubitza[1] and Kubitza[2] do not supply the missing teachings of the patented claims because neither reference, whether taken alone or in combination, teaches or suggests daily dosing with a rapid release dosage form over five consecutive days to a patient in need thereof. In response it is respectfully submitted that Kubitza et al.[1] teach administration of rivaroxaban orally once daily for five days and Kubitza et al.[2] teach rivaroxaban has a rapid onset of action, indicating the tablets are rapidly releasing the active compound.

Appellant argues that Kubitza[1] and Kubitza[2] are irrelevant to the presently claimed invention because they merely report studies of the "pharmacodynamics, safety, and pharmacokinetics" of rivaroxaban in "healthy male subjects" (see both

Kubitza abstract titles) and do no report studies of rivaroxaban in persons within the scope of the instant claims - patients in need of treatment or at a significantly increased risk for thromboembolic disorders - and thus cannot make obvious the presently claimed invention. Appellant further argues that the recitation of treating a patient "in need thereof" is well understood in the medical field to include patients having a significantly increased risk of the disease for which treatment is needed - in this case thromboembolism. A healthy volunteer, such as those used in the Kubitza, do not have an increased coagulation risk compared to those, i.e. under hip or knee replacement surgery. Thus, even when treatment includes prophylactic treatment of thromboembolic disorders, a patient in need thereof involves only patients with or at a heightened risk for thromboembolism, and not the healthy volunteers used in the Kubitza[1] and Kubitza[2] studies. In response it is respectfully submitted that Kubitza[1] and Kubitza[2] both teach the intended use of rivaroxaban is for the prevention and treatment of thromboembolic disorders. Thus, Kubitza[1] and Kubitza[2] clearly suggest administration to the instantly claimed patient population because it obvious to administer said drug for its intended use. As stated by the Appellant, anticoagulant drugs are not initially tested in sick patients for ethical reasons. However, after testing the safety of a given anticoagulant drug, it is obvious to administer said drug for its intended use of treating thromboembolism to a patient in need thereof.

Appellant further argues that Kubitza[1] and Kubitza[2] do not teach an efficacious dose would be a rapid-release oral dosage form administered once daily for five-consecutive days. Appellant argues that Kubitza[1] merely notes that rivaroxaban

"showed a rapid onset of action" but does not attribute this rapid onset of action to the oral dosage form. In response it is respectfully submitted that Kubitza[1] reports the results of rivaroxaban testing of two oral dosage forms: a solution and tablet. Since Kubitza[1] et al. teach that rivaroxaban has a rapid onset of action in the testing of these dosage forms, it is expected that the tablets did not contain any excipient that would delay the release of rivaroxaban, and subsequently the action of the rivaroxaban. Thus, the rivaroxaban tablets taught by Kubitza[1] must be rapid releasing the active compound.

Appellant argues that the Kubitza[1] and Kubitza[2] report a half-life for rivaroxaban (4-6 hours and 3-4 hours respectively) that would lead the ordinary artisan to expect that multiple daily dosages would be required. Appellant argues that it is well known to a person of ordinary skill in the art that a drug having a half-life of ten hours of less usually cannot be efficacious with once daily oral administration of a rapid release form. In response it is respectfully submitted that Kubitza[1] and Kubitza[2] teach once daily dosing of rapidly releasing tablets. Further, a once daily dosage of drug at a higher dosage is sometimes preferred in instant where patient compliance is an issue.

Appellant argues that one of ordinary skill in the art would have read Kubitza[2] as reporting early tests of a single administration to test safety, PK, and PD across a very broad range of amounts and would not found any teaching of what dosage in patients in need of treatment for or at increased risk of thromboembolic disorder, let alone that en efficacious dosage could be a once daily dosage in a rapid release dosage form over at least five days. In response to Appellant's arguments against the references individually, one cannot show nonobviousness by attacking references individually

where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). It is respectfully submitted that Kubitza et al.[1] teach administration of rivaroxaban orally once daily for five days and Kubitza et al.[2] teach rivaroxaban has a rapid onset of action, indicating the tablets are rapidly releasing the active compound.

Appellant argues that while Kubitza[1] and Kubitza[2] teach administration of rivaroxaban was safe and well-tolerated, this was in healthy volunteers rather than ill patients, and neither abstract suggests what dosage would be efficacious in preventing deep vein thrombosis or treating thromboembolisms generally in a person at heighted risk. Appellant argues that that Appellants are not comparing the efficacy of specific quantitative doses between Kubitza abstracts and the instant invention, but are pointing out that the Kubitza abstract do not disclose any efficacious dose relevant to treatment of persons encompassed by the instant claims by virtue of having tested healthy people. In response it is respectfully submitted that the instant claims do not require a particular dosage of rivaroxaban. Further, Kubitza[1] and Kubitza[2] both teach once daily dosing of rivaroxaban, which as explained in detail *supra*, is intended to be used for the treatment and/or prevention of thromboembolic events or disease.

C. Appellant argues with regard to the rejection of claims 1, 4, 5, 11, and 18 under 35 U.S.C. 103(a) as being unpatentable over Straub et al. (US 2003/0153610 A1) in view of in view of Kubitza[1] and Kubitza[2] that the for the same reasons as discussed in Section B., Kubtiza[1] and Kubitza[2] do not disclose that once daily oral dosaging of a

rapid-release form of rivaroxaban for at least five consecutive days would be efficacious in patients in need thereof because the Kubitza references disclose administration of rivaroxaban in healthy patients. In response it is respectfully submitted that as described in detail *supra* in Section B., Kubitza[1] and Kubitza[2] both teach the intended use of rivaroxaban is for the prevention and treatment of thromboembolic disorders and it is obvious to administer said drug for its intended use.

Appellant further argues that for the same reasons as discussed in section B., the person of ordinary skill in the art would not have been motivated to modify the dosages taught for once daily administration of a rapid-release form, nor would the person have expected such a treatment regimen to be successful because of the half-life of rivaroxaban and the lack of efficacy testing in ill patients. In response it is respectfully submitted that, as described *supra* in detail in Section B, Kubitza et al.[1] teach administration of rivaroxaban orally once daily for five days and Kubitza et al.[2] teach rivaroxaban has a rapid onset of action, indicating the tablets are rapidly releasing the active compound. One of ordinary skill in the art would have had a reasonable expectation of success in treating deep venous thromboses in a patient by administering rivaroxaban as taught by Straub et al. using the administration guidelines and tablets taught by Kubitza et al.[1] and Kubitza et al.[2] because rivaroxaban is known to treat deep venous thromboses, and Kubitza et al.[1] and Kubitza et al.[2] teach administration guidelines for rivaroxaban that are safe and tolerable for patients.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Jody L. Karol/

Examiner, Art Unit 1627

Conferees:

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1627

/Johann R. Richter/

Supervisory Patent Examiner, Art Unit 1621

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	
Misselwitz, Frank et al.	Group Art Unit: 1627
Application No.: 11/883,218	Examiner: Karol, Jody Lynn
Filed: July 16, 2008	Confirmation No.: 9960
For: Prevention and Treatment of Thromboembolic Disorders	

STATUS INQUIRY

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Madam:

Please advise, in writing, as to the current status of the above-captioned application.

Date: July 16, 2013

Respectfully submitted,

Christine Hansen

Christine M. Hansen
Registration No.: 40,634
BUCHANAN INGERSOLL & ROONEY PC
1005 North Market Street, Ste. 1900
Wilmington, Delaware 19801
(302) 552-4249
(302) 552-4295 (Fax)
Attorney for Applicant

Customer No. 21839

#1057132

Electronic Acknowledgement Receipt

EFS ID:	16328240
Application Number:	11883218
International Application Number:	
Confirmation Number:	9960
Title of Invention:	Prevention and Treatment of Thromboembolic Disorders
First Named Inventor/Applicant Name:	Frank Misselwitz
Customer Number:	21839
Filer:	Christine Hansen/Melissa Seebaran
Filer Authorized By:	Christine Hansen
Attorney Docket Number:	11987-00042
Receipt Date:	16-JUL-2013
Filing Date:	16-JUL-2008
Time Stamp:	13:58:21
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	Status_Inquiry.pdf	50693 43075bd15f5f52e451a68148fb2926242101564d	no	1
Warnings:					
Information:					

Total Files Size (in bytes):	50693

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
11/883,218	07/16/2008	Frank Misselwitz	11987-00042

CONFIRMATION NO. 9960

POWER OF ATTORNEY NOTICE

23416
CONNOLLY BOVE LODGE & HUTZ, LLP
P O BOX 2207
WILMINGTON, DE 19899

OC000000058561764

Date Mailed: 01/11/2013

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 01/08/2013.

- The Power of Attorney to you in this application has been revoked by the assignee who has intervened as provided by 37 CFR 3.71. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

/nmohammed/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
11/883,218	07/16/2008	Frank Misselwitz	11987-00042

CONFIRMATION NO. 9960

21839
BUCHANAN, INGERSOLL & ROONEY PC
POST OFFICE BOX 1404
ALEXANDRIA, VA 22313-1404

POA ACCEPTANCE LETTER

OC000000058561807

Date Mailed: 01/11/2013

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 01/08/2013.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

/nmohammed/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

PTO/SB/80 (11-08)
Approved for use through 11/30/2011. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

POWER OF ATTORNEY TO PROSECUTE APPLICATIONS BEFORE THE USPTO

I hereby revoke all previous powers of attorney given in the application identified in the attached statement under 37 CFR 3.73(b).

I hereby appoint:

☑ Practitioners associated with the Customer Number: 21839

OR

☐ Practitioner(s) named below (if more than ten patent practitioners are to be named, then a customer number must be used):

Name	Registration Number	Name	Registration Number

as attorney(s) or agent(s) to represent the undersigned before the United States Patent and Trademark Office (USPTO) in connection with any and all patent applications assigned only to the undersigned according to the USPTO assignment records or assignment documents attached to this form in accordance with 37 CFR 3.73(b).

Please change the correspondence address for the application identified in the attached statement under 37 CFR 3.73(b) to:

☑ The address associated with Customer Number: 21839

OR

☐ Firm or Individual Name			
Address			
City		State	Zip
Country			
Telephone		Email	

Assignee Name and Address:

BAYER INTELLECTUAL PROPERTY GMBH
Alfred-Nobel-Strasse 10
40789 Monheim Germany

A copy of this form, together with a statement under 37 CFR 3.73(b) (Form PTO/SB/96 or equivalent) is required to be filed in each application in which this form is used. The statement under 37 CFR 3.73(b) may be completed by one of the practitioners appointed in this form if the appointed practitioner is authorized to act on behalf of the assignee, and must identify the application in which this Power of Attorney is to be filed.

SIGNATURE of Assignee of Record

The individual whose signature and title is supplied below is authorized to act on behalf of the assignee

Signature		Date 2012-11-06
Name	Dr. Markus Albers / Dr. Alexander Nowak	Telephone
Title	Senior Patent Counsel / Senior Patent Counsel	

PTO/SB/96 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: BAYER INTELLECTUAL PROPERTY GMBH

Application No./Patent No.: 11/883,218 Filed/Issue Date: July 16, 2008

Titled:
PREVENTION AND TREATMENT OF THROMBOEMBOLIC DISORDERS

BAYER INTELLECTUAL PROPERTY GMBH , a Corporation
(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.

states that it is:

1. ☒ the assignee of the entire right, title, and interest in;

2. ☐ an assignee of less than the entire right, title, and interest in
(The extent (by percentage) of its ownership interest is _____ %); or

3. ☐ the assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made)

the patent application/patent identified above, by virtue of either:

A. ☐ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy therefore is attached.

OR

B. ☒ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: INVENTORS To: BAYER HEALTHCARE AG
The document was recorded in the United States Patent and Trademark Office at
Reel 020979 , Frame 0627 , or for which a copy thereof is attached.

2. From: BAYER HEALTHCARE AG To: BAYER SCHERING PHARMA AG
The document was recorded in the United States Patent and Trademark Office at
Reel 022575 , Frame 0337 , or for which a copy thereof is attached.

3. From: BAYER SCHERING PHARMA AG To: BAYER PHARMA AKTIENGESELLSCHAFT
The document was recorded in the United States Patent and Trademark Office at
Reel 029418 , Frame 0001 , or for which a copy thereof is attached.

☒ Additional documents in the chain of title are listed on a supplemental sheet(s).

☒ As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/Christine M Hansen/ January 8, 2013
Signature Date

Christine M. Hansen Attorney
Printed or Typed Name Title

4. From: BAYER PHARMA AKTIENGESELLSCHAFT To: BAYER INTELLECTUAL PROPERTY GMBH

The document was recorded in the United States Patent and Trademark Office at

Reel 029277, Frame 0713, or for which a copy of thereof is attached.

Electronic Acknowledgement Receipt

EFS ID:	14638318
Application Number:	11883218
International Application Number:	
Confirmation Number:	9960
Title of Invention:	Prevention and Treatment of Thromboembolic Disorders
First Named Inventor/Applicant Name:	Frank Misselwitz
Customer Number:	23416
Filer:	Christine Hansen/Lana Strawderman
Filer Authorized By:	Christine Hansen
Attorney Docket Number:	11987-00042
Receipt Date:	08-JAN-2013
Filing Date:	16-JUL-2008
Time Stamp:	09:17:29
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Power of Attorney	PowerOfAttorney.pdf	89137 eaf6c2525fc87bbd03cf8b888038069d8b70dfee	no	1

Warnings:	
Information:	

2	Assignee showing of ownership per 37 CFR 3.73.	0081565-000006.pdf	77881 afaf2ff5cfaf06691bfc7ee0f2a4095b99a5273d	no	2

Warnings:	
Information:	
Total Files Size (in bytes):	167018

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/883,218	07/16/2008	Frank Misselwitz	11987-00042	9960

23416 7590 05/23/2012
CONNOLLY BOVE LODGE & HUTZ, LLP
P O BOX 2207
WILMINGTON, DE 19899

EXAMINER	
KAROL, JODY LYNN	

ART UNIT	PAPER NUMBER
1627	

MAIL DATE	DELIVERY MODE
05/23/2012	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Examiner-Initiated Interview Summary	Application No.	Applicant(s)	
	11/883,218	MISSELWITZ ET AL.	
	Examiner	Art Unit	
	JODY KAROL	1627	

All participants (applicant, applicant's representative, PTO personnel):

(1) *JODY KAROL*. (3)_____.

(2) *Christine Hansen*. (4)_____.

Date of Interview: *16 May 2012*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☐103 ☐Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *1*.

Identification of prior art discussed: _____.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

Attempted to gain authorization for Examiner's amendment to insert the exemplified dosage of 30 mg into claim 1 in order to advance prosecution. The Examiner explained that the instant specification provided a single example of a once daily dosage of rivaroxaban exhibiting the alleged characteristics of the instant invention. The proposal was declined.

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/Yong S. Chong/ Primary Examiner, Art Unit 1627	

Docket No.: 11987-00042-US
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Frank Misselwitz et al.

Application No.: 11/883,218 | Confirmation No.: 9960

Filed: July 16, 2008 | Art Unit: 1627

For: PREVENTION AND TREATMENT OF THROMBOEMBOLIC DISORDERS | Examiner: Jody Lynn Karol

BRIEF ON APPEAL

TABLE OF CONTENTS

Docket No.: 11987-00042-US
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Frank Misselwitz et al.

Application No.: 11/883,218 | Confirmation No.: 9960

Filed: July 16, 2008 | Art Unit: 1627

For: PREVENTION AND TREATMENT OF THROMBOEMBOLIC DISORDERS | Examiner: Jody Lynn Karol

APPEAL BRIEF UNDER 37 C.F.R. § 41.37

MS Appeal Brief – Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Appellants hereby appeal the Examiner's decision finally rejecting claims 1, 4, 5, 11 and 18, as set forth in the Office Action of September 21, 2011 and in the Advisory Action dated February 10, 2012. A Notice of Appeal was timely filed on February 21, 2012, together with a Petition for a Two-Month Extension of Time. Pursuant to 37 C.F.R. § 41.37(a) and § 1.7(a), this brief is filed following the filing of the Notice of Appeal with the required fee pursuant to 37 C.F.R. § 41.20(b)(2) and § 1.7(a), paid by credit card.

I. REAL PARTY IN INTEREST

The real party in interest in this application is Bayer Pharma Aktiengesellschaft of Berlin, Germany. The current assignee of record is Bayer Schering Pharma AG ("Bayer") of Berlin, Germany, which since the last assignment recordation has changed its name to Bayer Pharma Aktiengesellschaft.

II. SUMMARY OF CLAIMED SUBJECT MATTER

Of the five claims on appeal, claim 1 is an independent claim.

Independent claim 1 relates to a method for treating (see *e.g.*, Specification at page 1, lines 2-5; page 3, lines 19-20; page 9, lines 1-2) a thromboembolic disorder (see *e.g.*, *id.* at page 1, lines 3 and 19-28; page 9, lines 6-25), comprising administering a direct factor Xa inhibitor (see *e.g.*, *id.* at page 1, lines 3 and 14-18; page 2, lines 20-29; page 9, lines 3-5) that is 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide (see *e.g.*, *id.* at page 3, lines 27-32 to page 4, lines 1-5; page 10, lines 10-13) no more than once daily for at least five consecutive days (see *e.g.*, *id.* at page 3, lines 19-26; page 10, lines 18-20) in a rapid-release oral dosage form (see *e.g.*, *id.* at page 3, line 21; page 10, lines 3-9) to a patient in need thereof (see *e.g.*, *id.* at page 1, line 4; page 2, line 32; page 3, lines 4-6 page 15, lines 15-22).

Claims 5 and 11 depend from claim 4, which depends from claim 1 and further recites that the thromboembolic disorder is ST Segment Elevation Myocardial Infarction (STEMI), Non ST Segment Elevation Myocardial Infarction (NSTEMI), unstable angina, reocclusion after angioplasty or aortocoronary bypass, pulmonary embolisms, deep vein thromboses or stroke (see *e.g.*, *id.* at page 9, lines 6-16). Claim 5 further recites that the oral dosage form is a rapid-release tablet (see *e.g.*, *id.* at page 10, lines 4-13). Claim 11 further recites that the thromboembolic disorder is Non ST Segment Myocardial Infarction (NSTEMI) (see *e.g.*, *id.* at page 9, lines 6-8 and lines 26-30).

Claim 18 depends from claim 1 and further recites that the thromboembolic disorder is deep vein thromboses (see *e.g.*, *id.* at page 9, lines 6-11, lines 17-18 and lines 26-30).

III. ARGUMENT

Claim 1 is the sole independent claim. Claims 5 and 11 depend from claim 4, which further depends from claim 1. Claim 18 depends directly from claim 1. Each rejected claim therefore incorporates by reference all the limitations of independent claim 1. Thus, the claims will be argued in one group throughout.

A. Are claims 1, 4, 5, 11, and 18 unpatentable under the doctrine of double patenting for not being patentably distinct from claims 13, 24, and 30 of U.S. Patent No. 7,157,456 or claims 1-6 and 17-21 of U.S. Patent No. 7,592,339?

Claims 1, 4, 5, 11, and 18 are rejected under the doctrine of double patenting for allegedly not being patentably distinct from claims 13, 24, and 30 of U.S. Patent No. 7,157,456

("the '456 patent") or claims 1-6 and 17-21 of U.S. Patent No. 7,592,339[1] ("the '339 patent") because the patented claims allegedly disclose the instantly claimed methods. (See September 21, 2011 Final Office Action at pages 7-8, paragraphs 8-9). Specifically, the Examiner asserts that "the instant claims and the patented claims are both directed to methods of treating thromboembolic disorders comprising administering 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-mopholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide (rivaroxaban)" (Final Office Action at pages 7-8). To the contrary, the instant claims are patentably distinct from claims 13, 24, and 30 of the '456 patent and claims 1-6 and 17-21 of the '339 patent because none of the patented claims cited by the Examiner teach, disclose, or suggest each element of the instantly claimed invention.

The present invention concerns the novel and surprising discovery that rivaroxaban can be efficacious with only once daily dosing for at least five days with a rapid release oral dosage form. (See *e.g.*, Specification at page 3, lines 15-22; page 4 lines 10-18; claim 1). The patented claims only disclose rivaroxaban and its use to treat and prevent thromboembolic disorders; they do not disclose the dosage frequency or form.[2] More pointedly, the patented claims do not disclose a (1) once daily treatment of rivaroxaban (2) for at least five days (3) in a rapid-release oral dosage form. The Examiner even recognizes this in the same Office Action. (Final Office Action at page 10) (the "patented claims do not teach administering [rivaroxaban] once daily for five consecutive days . . . . or that the dosage form is a rapid release form."). Because the patented claims do not mention these parameters, they cannot be found to suggest that such a therapy would be medically effective. For this reason, Appellants respectfully submit that the patented claims do not render obvious the present claims. Thus, the present claims are patentably distinct from the patented claims.

Appellants additionally refer to and incorporate by reference the following discussion concerning nonstatutory obviousness-type double patenting and statutory obviousness at Sections III.B-C. That discussion further explains why the claimed once daily dosaging is not

---

[1] The Examiner mistakenly identified U.S. Patent No. 7,592,339 as U.S. Patent No. 7,592,399 during prosecution. For clarity, the correct patent number is used herein.

[2] For example, claim 13 of the '456 patent recites: "A method for treatment of a thromboembolic disorder comprising administering to a patient in need thereof an effective amount of [rivaroxaban], wherein the thromboembolic disorder is myocardial infarct, pulmonary embolism or deep venous thrombosis." Claim 1 of the '339 patent recites: "A method for inhibiting thrombus formation comprising administering an effective amount of [rivaroxaban], to a patient in need of said method."

obvious, and therefore why it is patentably distinct from the cited claims of the '456 and '339 patents.

For all these reasons, reversal of the double patenting rejection of claims 1, 4, 5, 11, and 18 based on claims 13, 24, and 30 of U.S. Patent No. 7,157,456 and claims 1-6 and 17-21 of U.S. Patent No. 7,592,339 is respectfully requested.

B. Are claims 1, 4, 5, 11, and 18 unpatentable under the doctrine of nonstatutory obviousness-type double patenting based on claims 13, 24, and 30 of U.S. Patent No. 7,157,456 or claims 1-6 and 17-21 of U.S. Patent No. 7,592,339 in view of the Kubitza[1] and Kubitza[2] references?

Claims 1, 4, 5, 11, and 18 are rejected under the doctrine of nonstatutory obviousness-type double patenting as allegedly being obvious over the same claims of the '456 and '339 patents discussed above in view of Kubitza *et al.,* "Multiple Dose Escalation Study Investigating the Pharmacokinetics, Safety, and Pharmacokinetics of BAY 59-7939 an Oral, Direct Factor Xa Inhibitor in Healthy Male Subjects," (Blood, vol. 102:11, Abstract No. 3004, 16 November 2003, p. 811a) ("Kubitza[1]") and Kubitza *et al.*, "Single Dose Escalation Study Investigating the Pharmacodynamics, Safety, and Pharmacokinetics of BAY 59-7939 an Oral, Direct Factor Xa Inhibitor in Healthy Male Subjects," (Blood, vol. 102:11, Abstract No. 3010, 16 November 2003, p. 813a) ("Kubitza[2]").

The Examiner relies on the same claims of the '456 and '339 patents discussed above for disclosing rivaroxaban to treat thromboembolic disorders. (See Final Office Action at page 10). But, as acknowledged by the Examiner and as discussed in Section VII.A above, the patented claims do not disclose the presently claimed once daily dosage for at least five consecutive days in a rapid-release oral dosage form. The Examiner relies on the Kubitza references for this missing teaching. Specifically, the Examiner relies on Kubitza[1] for "administering 5 mg of BAY 59-7939 (rivaroxaban) once daily to male subjects on day 0 and days 4-8 . . . ." and Kubitza[2] for administering rivaroxaban "as a tablet to men, wherein [rivaroxaban] showed rapid onset of action (i.e., rapid release) . . . . [and was] safe and well tolerated across a wide range of oral doses." (Final Office Action at pages 10, 12-13). The Examiner then asserts that the instant methods would have been obvious to one of skill based on the motivation to combine and the expectation of success allegedly supplied by the Kubitza references. Appellants respectfully disagree. Kubitza[1] and Kubitza[2] do not supply the missing teachings of the patented claims

because neither reference, whether taken alone or in combination, teaches or suggests once daily dosing with a rapid release dosage form over five consecutive days to a patient in need thereof.

First, the disclosures of Kubitza[1] and Kubitza[2] are irrelevant to the presently claimed invention because they merely report studies of the "pharmcodynamics, safety, and pharmacokinetics" of rivaroxaban in "healthy male subjects." (See both Kubitza abstract titles). They do not report studies of rivaroxaban dose efficacy in persons within the scope of the instant claims – patients in need of treatment for or at a significantly increased risk for thromboembolic disorders – and thus cannot make obvious the presently claimed invention.

The art of developing a safe and efficacious dosage regimen for a drug involves many steps after a molecule is identified as having biological activity. In the initial human trials, healthy volunteers are used to evaluate the safety, pharmacokinetic (PK), and pharmacodynamic (PD) properties of the drug. This information is useful to later design of dosage trials for subsequent efficacy studies using volunteers with relevant predetermined medical conditions. The drug is not initially tested in sick patients because it is better to test in healthy volunteers with no known risk factors for disease who are at the least risk of being harmed by an incorrect dose. Furthermore, anticoagulant dosage trials may not begin with ill patients that require an anticoagulant. Such patients cannot be treated ethically with a drug at a dosage that has not been shown to work or at a dosage so high that it may cause an unacceptable degree of bleeding. These patients also cannot be given a placebo in dosage trials for similar ethical reasons. Thus, patients requiring an anticoagulant cannot be the initial subjects for testing dosages of a new anticoagulant.

Both Kubitza[1] and Kubitza[2] report the results of some of the very first rivaroxaban dosage testing in healthy human volunteers. The Kubitza abstracts report tests investigating the safety, PK, and PD properties of rivaroxaban as the abstract titles clearly indicate. Kubitza[2] reports the results of administering a single dose only of rivaroxaban to healthy volunteers in either a tablet or oral solution dosage form. Each volunteer only received one dose, and the dosages varied among the different volunteers. Notably, Kubitza[2] observes that rivaroxaban demonstrated a "rapid onset of action," but does not correlate this effect to the oral tablet dosage form. (See Kubitza[2] at line 5). Kubitza[1] reports a multiple dose escalation study in healthy human volunteers in which six different dosage regimens were tested for five days each. Only one of these dosing regimens involved a once daily dosage, and that was in the lowest overall

dosage amount (5 mg) tested. (See Kubitza[1] at lines 3-4: "64 subjects received multiple oral doses of BAY 59-7939: 5 mg od, bid, or tid, or 10 mg, 20 mg, or 30 mg bid for five days with food."). However, neither Kubitza abstract discusses what dosage would be efficacious in patients suffering from, or at risk for, a thromboembolic disorder. Indeed, they cannot teach efficacious dosages because they report results in healthy patients who are not at a heightened risk for thromboembolism. One of ordinary skill in the art cannot determine the efficacy of a dose of a given drug with healthy volunteers.

The Examiner asserted in the Final Office Action that healthy subjects are encompassed by the instant claims because the specification defines "treatment" to include "prophylactic treatment of thromboembolic disorders." (Final Office Action at pages 4-5). The Examiner thus interpreted "the patient population ... to include healthy subjects since anyone could potentially be at risk for deep vein thrombosis." (Final Office Action at page 5). The Examiner's interpretation is improper because it fails to consider the meaning and effect of the phrase "to a patient in need thereof." See *In re Wilson*, 424 F.2d 1382, 1385 (CCPA 1970) ("All the words in a claim must be considered in judging the patentability of that claim against the prior art."); MPEP § 2111.01 ("The words of a claim must be given the[] plain meaning . . . . the ordinary and customary meaning given to the term by those of ordinary skill in the art.").

The claims recite treating a patient "in need thereof." That term is well understood in the medical field to include patients having a significantly increased risk of the disease or condition for which treatment is needed – in this case, thromboembolism. For example, prophylaxis with rivaroxaban is advised for patients undergoing hip or knee replacements. Surgical interventions activate the coagulation system which, depending on the type of surgery, increases the risk of clot formation not only at the site of the surgical wound, but also elsewhere in the body. Hip and knee replacement surgery are known to have a high risk of inducing this clot formation in the lower extremities. A healthy volunteer such as those used in the Kubitza studies is not undergoing hip or knee replacement and does not have this increased coagulation risk. Also, rivaroxaban is indicated for reducing the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. (See Xarelto® rivaroxaban prescribing information of November 2011, attached to Appellants' January 30, 2012 Amendment and Response to the Final Office Action). This condition involves an increased risk of blood pooling leading to clot formation in the heart, and thus thromboembolisms. These indications are just two examples of the many

possible prophylactic uses for rivaroxaban. Prophylaxis for thromboembolism in a patient in need thereof therefore involves a patient at a heightened risk for thromboembolism above that of a normal person, and not the healthy volunteers used in the Kubitza[1] and Kubitza[2] studies.

The Examiner's assumption that healthy people would be within the patient population of the present claim is also incorrect because one of ordinary skill in the art would not distort the normal haemostasis of a healthy person by administering an anticoagulant unnecessarily. "Maintenance of normal haemostasis – the balance between bleeding and thrombosis – is subject to complex regulatory mechanisms." (Specification at page 1, lines 19-20). Administration of an anticoagulant involves balancing the increased need to prevent coagulation such as clot formation in a patient in need thereof with the increased risk of uncontrolled bleeding from the anticoagulant. Improper interference with the coagulation system can cause various thromboembolic disorders. (See Specification at page 2, lines 20-28). The Examiner's interpretation of the phrase "in need thereof" makes a leap in reasoning that ignores these concerns. Prophylactic treatment for a disease in a patient "in need thereof" logically excludes treatment of healthy people having no increased risk for a given disease because such people are not patients "in need" of treatment for that disease. Moreover, because the claims recite "treating a thromboembolic disorder" in "a patient in need thereof," one of ordinary skill would understand that treatment of a thromboembolic disorder – even including prophylaxis – is only for a person with increased risk of thromboembolism. Thus, the Kubitza abstracts do not disclose treatment of persons within the scope of the present claims.

Second, neither Kubitza abstract discloses that an efficacious dose would be a rapid-release dosage oral dosage form administered once daily for five consecutive days. The Examiner asserted that Kubitza[2] teaches that "rivaroxaban has a rapid onset of action, indicating the tablets are rapidly releasing the active compound." (Final Office Action at page 5). The Examiner then asserted in the February 10, 2012 Advisory Action that "Kubitza[1] and Kubitza[2] both teach once daily dosing of rapidly releasing tablets." (Advisory Action at PTO-303 Continuation Sheet, lines 10-11). Kubitza[2] nowhere notes any rapid onset of action for rivaroxaban. Kubitza[1] merely notes that rivaroxaban "showed a rapid onset of action." (Kubitza[1] at line 5). However, Kubitza[1] reports the results of rivaroxaban testing involving two oral dosage forms: a tablet and a solution. Kubitza[1] nowhere attributes this rapid onset of action to the oral tablet dosage form.

Additionally, both Kubitza abstracts report a half-life for rivaroxaban that would lead the ordinary artisan to expect that multiple daily dosages would be required. Specifically, when a "drug substance is applied in no more than a therapeutically effective amount, which is usually preferred in order to minimize the exposure of patients with that drug substance in order to avoid side effects, the drug must be given approximately every half-life." (Specification at page 3, lines 4-8, citing Malcolm Rowland and Thomas Tozer, "Clinical Pharmacokinetics," 1995, p. 83). It is well known to a person of ordinary skill in the art that a drug having a half-life of ten hours or less usually cannot be efficacious with once daily oral administration of a rapid release form. (See, *e.g.*, Specification at page 3, lines 15-18). Both Kubitza[1] and Kubitza[2] report half-lives for rivaroxaban that would indicate multiple daily dosages were required: Kubitza[2] reports a half-life of 4-6 hours while Kubitza[1] reports a half-life of 3-4 hours. Therefore, one of skill in the art would not have been motivated to administer rivaroxaban only once daily and in a rapid-release dosage form because successful therapy would not have been expected.

The Examiner asserts that the skilled person would have been motivated to administer rivaroxaban once daily using the rapid release tablet of Kubitza[2] for patient convenience and compliance. (Final Office Action at page 11). Again, and for the reasons above, Appellants disagree. The ordinary skilled person would have read Kubitza[2] as reporting early tests of a ***single administration*** of rivaroxaban to 103 healthy volunteers in order to test safety, PK, and PD across a very broad range of dosage amounts. This ordinary person would not have found any teaching from Kubitza[2] of what dosage would be efficacious in patients in need of treatment for or at an increased risk of a thromboemobolic disorder, let alone that an efficacious dosage could be a once daily dosage in a rapid release dosage form over at least five days.

The Examiner also asserts that the ordinary skilled person would have had a reasonable expectation of successfully treating deep vein thrombosis by administering rivaroxaban once daily in a rapid release dosage form because Kubitza[1] and Kubitza[2] teach administration guidelines for rivaroxaban that are safe and tolerable for patients. (Final Office Action at page 11). Again, although both abstracts admittedly report that rivaroxaban was safe and well tolerated, this was in healthy volunteers rather than ill patients, and neither abstract suggests efficacious dosages for preventing deep vein thrombosis or generally treating thromboembolic disorders in a person at heightened risk therefor. The Examiner dismissed this argument in the Advisory Action and maintained the rejection, responding: "the instant claims do not require a

particular dosage of rivaroxaban." (Advisory Action at PTO-303 Continuation Sheet, lines 14-15). The Examiner misses the point.

Appellants are not comparing the efficacy of specific quantitative doses between the Kubitza abstracts and the instant invention. Instead, Appellants' point is that the Kubitza abstracts do not disclose any efficacious dose relevant to treatment of persons encompassed by the instant claims by virtue of having tested healthy people, as discussed in detail above. The instant claims do not recite a specific quantitative dose (*i.e.*, in milligrams) because, as previously noted, the instant invention relates to the novel discovery that rivaroxaban can be efficacious in certain dosage *forms* (*i.e.*, using once daily dosing for at least five days in a rapid release oral dosage form), aside from its efficaciousness in any given dosage amount. For the reasons above, the Kubitza abstracts do not disclose any dosage and teach that it is efficacious for persons in need of treatment for or at increased risk of a thromboembolic disorder. Therefore, one of skill in the art would not have had a reasonable expectation of success.

For all these reasons, reversal of the nonstatutory obviousness-type double patenting rejection of claims 1, 4, 5, 11, and 18 based on the '456 and '339 patents in view of the Kubitza[1] and Kubitza[2] references is respectfully requested.

C. Are claims 1, 4, 5, 11, and 18 unpatentable under 35 U.S.C. § 103(a) as being obvious over U.S. Patent Pub. No. 2003/0156310 A1 in view of the Kubitza[1] and Kubitza[2] references?

Claims 1, 2, 4-6 and 9-14 are rejected under 35 U.S.C. § 103(a) as being obvious over Straub *et al.*, U.S. Patent Pub. 2003/0153610[3] ("Straub") in view of Kubitza[1] and Kubitza[2]. The Examiner alleges that Straub teaches "oxazolidinone derivatives [including rivaroxaban] for the treatment of thromboembolic disorders including deep vein thrombosis." (Final Office Action at page 15). The Examiner further alleges that Straub teaches "oral administration . . . wherein oral formulations include tablets." (*Id.*). The Examiner acknowledges that Straub does not teach "administering [rivaroxaban] once daily for at least five consecutive days," or "the plasma concentration half-life [of rivaroxaban] in a human patient," or even "a rapid release tablet as claimed in the instant claim 5." (*Id.* at 15-16). However, the Examiner relies on Kubitza[1] for teaching "administering 5 mg of [rivaroxaban] once daily . . . for 4-8 days." (*Id.* at 16). In

[3] Straub *et al.* is the published application that resulted in the granted '456 patent discussed in the double patenting rejections above. Also, for clarity, the Examiner transposes two numbers in the Straub *et al.* publication number, U.S. 2003/015**63**10, but the correction is obvious so we address the published application 2003/015**36**10.

addition, the Examiner relies on Kubitza[2] for teaching "administering 1.25 mg to 80 mg of [rivaroxaban] under fasting conditions as a tablet to men, wherein [rivaroxaban] showed rapid onset of action (i.e., rapid release)," and that rivaroxaban "is safe and well-tolerated across a wide range of oral doses (1.25 mg to 80 mg)." (*Id.*). From this, the Examiner concludes that it would have been prima facie obvious to one of skill in the art to treat a thromboembolic disorder by administering rivaroxaban no more than once daily for at least five consecutive days in a rapid-release oral dosage form to a patient in need thereof. (*Id.* at 16-17). Appellants disagree.

For the reasons discussed above in Section III.B, Kubitza[1] and Kubitza[2] do not disclose that once daily oral dosaging of a rapid-release form of rivaroxaban for at least five consecutive days would be efficacious in patients in need thereof because the Kubitza references disclose administration of rivaroxaban to healthy subjects. The initial safety, PK, and PD testing reporting by the Kubitza abstracts does not inform the dosaging efficacy of rivaroxaban in patients suffering from, or at risk for, a thromboembolic disorder.

Furthermore, for the same reasons discussed above, the person of ordinary skill in the art would not have been motivated to modify the dosages taught for once daily administration of a rapid-release form, nor would the person have expected such a treatment regimen to be successful because of the half-life of rivaroxaban and the lack of efficacy testing in ill patients. Contrary to the Examiner's conclusions, a reasonable expectation of success with the claimed dosing regimen and form cannot be found in the Kubitza[1] and Kubitza[2] disclosures of safe and tolerable dosages in healthy people when the art has accepted the primacy of pharmacokinetic values such as half-life in determining a likely successful oral dosage regimen for patients in need of treatment.

Thus, for the same reasons provided above in Section III.B regarding the double patenting rejections involving Kubitza[1] and Kubitza[2], reversal of the obviousness rejection of claims 1, 4, 5, 11, and 18 is respectfully requested.

IV. CONCLUSION

In sum, for the reasons of record and the reasons discussed above, reversal of the double patenting rejections, nonstatutory obviousness-type double patenting rejections, and obviousness rejection under 35 U.S.C. § 103(a) of claims 1, 4, 5, 11, and 18 is respectfully requested.

This Appeal Brief is filed following the filing of the Notice of Appeal, which was filed on February 21, 2012, with the required fee pursuant to 37 C.F.R. § 41.20(b)(2) and § 1.7(a),

paid by credit card. Applicants also submit here with authorization to charge the fee for a brief under 37 C.F.R. § 41.20(b)(2) to the undersigned's credit card. No further fee is believed due. If a further fee is due for filing this appeal, please charge our Deposit Account No. 03-2775, under Order No. 11987-00042-US from which the undersigned is authorized to draw.

Respectfully submitted,

Date April 20, 2012

By Christine M. Hansen

Christine M. Hansen, Esq.
Registration No.: 40,634
CONNOLLY BOVE LODGE & HUTZ LLP
1007 North Orange Street
P. O. Box 2207
Wilmington, Delaware 19899-2207
(302) 658-6432
(302) 658-5614 (Fax)
Attorney for Applicants

EBF/lmc/4672965v3

APPENDIX OF CLAIMS

Claims Involved in the Appeal of Application Serial No. 11/883,218

1. A method of treating a thromboembolic disorder comprising administering a direct factor Xa inhibitor that is 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide no more than once daily for at least five consecutive days in a rapid-release oral dosage form to a patient in need thereof.

2-3. (Cancelled).

4. The method of claim 1, wherein the thromboembolic disorder is ST Segment Elevation Myocardial Infarction (STEMI), Non ST Segment Elevation Myocardial Infarction (NSTEMI), unstable angina, reocclusion after angioplasty or aortocoronary bypass, pulmonary embolisms, deep vein thromboses or stroke.

5. The method of claim 1, wherein the oral dosage form is a rapid-release tablet.

6. (Cancelled).

7. (Withdrawn) A packaged pharmaceutical composition comprising a container containing a rapid-release tablet comprising 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide, said container furthermore containing instructions for using said rapid-release tablet to treat a thromboembolic disorder.

8. (Withdrawn) The packaged pharmaceutical composition of claim 7, comprising a container containing a rapid-release tablet comprising 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide, said container furthermore containing instructions for administering said rapid-release tablet at a frequency of once daily.

9. (Withdrawn) The method of claim 1, wherein the thromboembolic disorder is ST Segment Elevation Myocardial Infarction (STEMI).

10. (Cancelled).

11. The method of claim 4, wherein the thromboembolic disorder is Non ST Segment Elevation Myocardial Infarction (NSTEMI).

12-14. (Cancelled).

15. (Withdrawn) The method of claim 1, wherein the thromboembolic disorder is unstable angina.

16. (Withdrawn) The method of claim 1, wherein the thromboembolic disorder is reocclusion after angioplasty or aortocoronary bypass.

17. (Withdrawn) The method of claim 1, wherein the thromboembolic disorder is pulmonary embolisms.

18. The method of claim 1, wherein the thromboembolic disorder is deep vein thromboses.

19. (Withdrawn) The method of claim 1, wherein the thromboembolic disorder is stroke.

Electronic Patent Application Fee Transmittal

Application Number:	11883218
Filing Date:	16-Jul-2008
Title of Invention:	Prevention and Treatment of Thromboembolic Disorders
First Named Inventor/Applicant Name:	Frank Misselwitz
Filer:	Christine Hansen/Sara Maloney
Attorney Docket Number:	11987-00042

Filed as Large Entity

U.S. National Stage under 35 USC 371 Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Filing a brief in support of an appeal	1402	1	620	620
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**620**

Electronic Acknowledgement Receipt

EFS ID:	12591655
Application Number:	11883218
International Application Number:	
Confirmation Number:	9960
Title of Invention:	Prevention and Treatment of Thromboembolic Disorders
First Named Inventor/Applicant Name:	Frank Misselwitz
Customer Number:	23416
Filer:	Christine Hansen/Sara Maloney
Filer Authorized By:	Christine Hansen
Attorney Docket Number:	11987-00042
Receipt Date:	20-APR-2012
Filing Date:	16-JUL-2008
Time Stamp:	13:59:40
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$620
RAM confirmation Number	245
Deposit Account	
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1	Appeal Brief Filed	Appeal_Brief.pdf	833286 0305d3d1a82919c9c05f2db31e50bdd61be4b7e4	no	15
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30192 64dfdd5358a547e1559e4391f39de748628a1bc0	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	863478	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/31 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

NOTICE OF APPEAL FROM THE EXAMINER TO THE BOARD OF PATENT APPEALS AND INTERFERENCES	Docket Number (Optional) 11987-00042-US

In re Application of
Frank Misselwitz et al.

Application Number	Filed
11/883,218-Conf. #9960	July 16, 2008

For PREVENTION AND TREATMENT OF THROMBOEMBOLIC DISORDERS

Art Unit	Examiner
1627	Jody Lynn Karol

Applicant hereby **appeals** to the Board of Patent Appeals and Interferences from the last decision of the examiner.

The fee for this Notice of Appeal is (37 CFR 41.20(b)(1)) $ 620.00

☐ Applicant claims small entity status. See 37 CFR 1.27. Therefore, the fee shown above is reduced by half, and the resulting fee is: $ _____

☐ A check in the amount of the fee is enclosed.

☒ Payment by credit card.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. 03-2775 .

☒ A petition for an extension of time under 37 CFR 1.136(a) (PTO/SB/22) is enclosed.

WARNING: INFORMATION ON THIS FORM MAY BECOME PUBLIC. CREDIT CARD INFORMATION SHOULD NOT BE INCLUDED ON THIS FORM. PROVIDE CREDIT CARD INFORMATION AND AUTHORIZATION ON PTO-2038.

I am the

☐ applicant /inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)

☒ attorney or agent of record.
Registration number 40,634

☐ attorney or agent acting under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34. _____

/Christine M. Hansen/
Signature

Christine M. Hansen
Typed or printed name

(302) 658-9141
Telephone number

February 21, 2012
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of 1 forms are submitted.

#4,662,904

PTO/SB/22 (09-11)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless if displays a valid OMB control number.

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)	Docket Number (Optional) 11987-00042-US
Application Number 11/883,218-Conf. #9960	Filed July 16, 2008
For PREVENTION AND TREATMENT OF THROMBOEMBOLIC DISORDERS	
Art Unit 1627	Examiner Jody Lynn Karol

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

		Fee	Small Entity Fee	
☐	One month (37 CFR 1.17(a)(1))	$150	$75	$
☒	Two months (37 CFR 1.17(a)(2))	$560	$280	$
☐	Three months (37 CFR 1.17(a)(3))	$1270	$635	$
☐	Four months (37 CFR 1.17(a)(4))	$1980	$990	$
☐	Five months (37 CFR 1.17(a)(5))	$2690	$1345	$ 560.00

☐ Applicant claims small entity status. See 37 CFR 1.27.

☐ A check in the amount of the fee is enclosed.

☒ Payment by credit card.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 03-2775 .

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96).

☒ attorney or agent of record. Registration Number 40,634

☐ attorney or agent under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34 _____

/Christine M. Hansen/ — Signature
February 21, 2012 — Date

Christine M. Hansen — Typed or printed name
(302) 658-9141 — Telephone Number

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below.

☐ Total of 1 forms are submitted.

#4,662,908

Electronic Patent Application Fee Transmittal

Application Number:	11883218
Filing Date:	16-Jul-2008
Title of Invention:	Prevention and Treatment of Thromboembolic Disorders
First Named Inventor/Applicant Name:	Frank Misselwitz
Filer:	Christine Hansen/Sara Maloney
Attorney Docket Number:	11987-00042

Filed as Large Entity

U.S. National Stage under 35 USC 371 Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Notice of appeal	1401	1	620	620
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension - 2 months with $0 paid	1252	1	560	560
Miscellaneous:				
			Total in USD ($)	**1180**

Electronic Acknowledgement Receipt

EFS ID:	12120571
Application Number:	11883218
International Application Number:	
Confirmation Number:	9960
Title of Invention:	Prevention and Treatment of Thromboembolic Disorders
First Named Inventor/Applicant Name:	Frank Misselwitz
Customer Number:	23416
Filer:	Christine Hansen/Sara Maloney
Filer Authorized By:	Christine Hansen
Attorney Docket Number:	11987-00042
Receipt Date:	21-FEB-2012
Filing Date:	16-JUL-2008
Time Stamp:	14:48:22
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$1180
RAM confirmation Number	1318
Deposit Account	
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1	Notice of Appeal Filed	notice_appeal.pdf	57918 af022bd3ed91e18e7dcb6ab5fc7e84c992c4bc96	no	1
Warnings:					
Information:					
2	Extension of Time	EOT.pdf	56803 04034e324426ac36213e8452038dd8fb2b7b4838	no	1
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	32162 f696efd778887dcce8c2852c674ca81fdeb8f93e	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	146883		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/883,218	07/16/2008	Frank Misselwitz	11987-00042	9960

23416 7590 02/10/2012
CONNOLLY BOVE LODGE & HUTZ, LLP
P O BOX 2207
WILMINGTON, DE 19899

EXAMINER	
KAROL, JODY LYNN	

ART UNIT	PAPER NUMBER
1627	

MAIL DATE	DELIVERY MODE
02/10/2012	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 11/883,218	**Applicant(s)** MISSELWITZ ET AL.
	Examiner JODY KAROL	**Art Unit** 1627

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 30 January 2012 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *3* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1,4,5,11 and 18*.
   Claim(s) withdrawn from consideration: *7-9,15-17 and 19*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☒ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). 6/17/2011
13. ☐ Other: _____.

/Yong S. Chong/
Primary Examiner, Art Unit 1627

Continuation of 11. does NOT place the application in condition for allowance because: of the reasons of record in the 9/21/2011 Office action. Applicant argues that Kubitza1 and Kubitza2 do not discuss what dosage would be efficacious. In response it is respectfully submitted that the instant claims do not presently recite a dosage for rivaroxaban in the treatment of deep vein thrombosis. Applicant further argues that the instant claims do not include healthy patients in the patient population because a person of ordinary skill in the art would understand that the treatment or prophylaxis of a thromboemoblic disorder in "a patient in need thereof" is only for a person with increased risk of thromboemoblism. Applicants thus assert that Kubitza1 and Kubitza2 do not disclose treatment of persons within the scope of the invention. In response it is respectfully submitted that rivaroxaban is taught by Kubitza1 and Kubitza2 as for the prevention and treatment of thromboembolic disorders. Thus, Kubitza1 and Kubitza2 clearly suggest adminstration to the instantly claimed patient population. Applicant fruther argues that based on the half life for rivaroxaban, the ordinary artisan would expect that multiple daily dosages would be required. In response it is respectfully submitted that Kubitza1 and Kubitza2 both teach once daily dosing of rapidly releasing tablets. Further, a once daily dosage of a drug at a higher dosage is sometimes preferred in instances where patient compliance is an issue. Applicant argues that whlle admittedly both Kubitza1 and Kubitza2 report that rivaroxaban was safe and well tolerated, this was in healthy volunteers rather than ill patients, and neither abstract suggests what dosage would be efficacious in preventing deep vein thrombosis or treating thromboembolisms generally in a person at heightened risk. In response it is respectfully submitted that the instant claims do not require a particular dosageof rivaroxaban. Further, Kubitza1 and 2 both teach once daily dosing of rivaroxaban and that rivaroxaban is intended to be used for the treatment and/or prevention of thromboembolic events or diseases. Applicant aruges that the data in table 1-1 and 1-2 is not relied upon to show that once daiily dosaging was suprisingly superior to other dsoages tested, but rather that its effeicacy feel where on would have expected a bid dosage to be and its side effects also fell where a bid dosage was expected to be. Thus, the datat shows that once daily dosaging with rapid release dosage form was possible. In response it is respectfully submitted that a once daily dosaging with a rapid release form is obvious over the cited prior art. Further, one of ordinary skill in the art would have been motivated to use a once daily dosaging in order to improve patient compliance. It is also noted that the IDS submitted on 6/17/2011 has been reviewd again based upon Applicant's arguments and is resubmitted herein.

PTO/SB/08b (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	11/883,218-Conf. #9960
Filing Date	July 16, 2008
First Named Inventor	Frank Misselwitz
Art Unit	1627
Examiner Name	Jody Lynn Karol
Attorney Docket Number	11987-00042-US

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	CA	BREITENBACH, J. Feste Loesungen durch Schmelzextrusion - ein integriertes Herstellkonzept. Pharmazie in unserer Zeit 29 (2000), 46-49.	
	CB	Pschyrembel, Klinisches Worterbuch, 257. Auflage, 1994, Walter de Gruyter Verlag, p. 610, Stichwort "Heparin."	
	CC	Pschyrembel, Klinisches Worterbuch, 257. Auflage, 1994, Walter de Gruyter Verlag, p. 292, Stichwort "Cumarinderivate."	
	CD	Pschyrembel, Klinisches Worterbuch, 257. Auflage, 1994, Walter de Gruyter Verlag, p. 199-200, Stichwort "Blutgerinnung."	
	CE	Rompp Lexikon Chemie, Ver. 1.5, 1998, Georg Thieme Verlag Stuttgart, Stichwort "Heparin."	
	CF	Rompp Lexikon Chemie, Ver. 1.5, 1998, Georg Thieme Verlag Stuttgart, Stichwort "Blutgerrinung" Lubert Stryer, Biochemie, Spektrum der Wissenschaft Verlagsgesellschaft mbH Heidelberg, 1990, p. 259.	

Examiner Signature	/Jody Karol/	Date Considered	02/08/2012

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.K./

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.K./

Docket No.: 11987-00042-US
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Frank Misselwitz et al.

Application No.: 11/883,218 Confirmation No.: 9960

Filed: July 27, 2007 Art Unit: 1627

For: PREVENTION AND TREATMENT OF THROMBOEMBOLIC DISORDERS Examiner: Jody Lynn Karol

RESPONSE TO FINAL OFFICE ACTION

MS Final
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

INTRODUCTORY COMMENTS

Applicants respond to the final Office Action mailed September 21, 2011 as follows:

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 4 of this paper.

AMENDMENTS TO THE CLAIMS

1. (Currently amended) A method of treating a thromboembolic disorder comprising administering a direct factor Xa inhibitor that is 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide no more than once daily for at least five consecutive days in a rapid-release oral dosage form ~~or forms~~ to a patient in need thereof~~, wherein said inhibitor has a plasma concentration half life of 10 hours or less when orally administered to a human patient~~.

2. (Cancelled).

3. (Cancelled).

4. (Previously presented) The method of claim 1, wherein the thromboembolic disorder is ST Segment Elevation Myocardial Infarction (STEMI), Non ST Segment Elevation Myocardial Infarction (NSTEMI), unstable angina, reocclusion after angioplasty or aortocoronary bypass, pulmonary embolisms, deep vein thromboses or stroke.

5. (Currently amended) The method of claim 1, wherein the oral dosage form ~~or forms~~ is a rapid-release tablet.

6. (Cancelled)

7. (Withdrawn) A packaged pharmaceutical composition comprising a container containing a rapid-release tablet comprising 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide, said container furthermore containing instructions for using said rapid-release tablet to treat a thromboembolic disorder.

8. (Withdrawn) The packaged pharmaceutical composition of claim 7, comprising a container containing a rapid-release tablet comprising 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide, said

container furthermore containing instructions for administering said rapid-release tablet at a frequency of once daily.

9. (Withdrawn) The method of claim 1, wherein the thromboembolic disorder is ST Segment Elevation Myocardial Infarction (STEMI).

10. (Cancelled)

11. (Previously presented) The method of claim 4, wherein the thromboembolic disorder is Non ST Segment Elevation Myocardial Infarction (NSTEMI).

12-14 (Cancelled).

15. (Withdrawn) The method of claim 1, wherein the thromboembolic disorder is unstable angina.

16. (Withdrawn) The method of claim 1, wherein the thromboembolic disorder is reocclusion after angioplasty or aortocoronary bypass.

17. (Withdrawn) The method of claim 1, wherein the thromboembolic disorder is pulmonary embolisms.

18. (Previously presented) The method of claim 1, wherein the thromboembolic disorder is deep vein thromboses.

19. (Withdrawn) The method of claim 1, wherein the thromboembolic disorder is stroke.

REMARKS

Entry of Amendments

In response to the final Office Action, Applicants respectfully request entry of the above amendments to claims 1 and 5 because they respond to express rejections as to form and/or place the claims in better form for appeal. Specifically, the final Office Action rejected claims 1, 4, 5, 11 and 18 as indefinite for reciting "no more than once daily...oral dosage form or forms." The Office indicated that the inclusion of "or forms" was confusing as to the covered dosage. Applicants respectfully request that claim 1 and 5 be amended to remove reference to "or forms."

The intent behind including "forms" was to claim a once-daily method that includes simultaneous administration of multiple dosage forms, or consecutive administration of two or more dosage forms within a short time frame. However, the Office finds the addition of "or forms" unclear. Furthermore, it is not needed because the claims when read in view of the specification include methods having this use of multiple dosage forms. The specification defines once daily dosing as follows (p. 10 lines 18-20, emphasis added): "The term ***'once daily'*** is well known by those skilled in the art and means administration of the drug once a day and ***includes the administration of one dosage form as well as administration of two or more dosage forms simultaneously or consecutively within a short time period.***"

Applicants also respectfully request that claim 1 be amended to remove the wherein clause specifying that the direct factor Xa inhibitor have a plasma half life of ten hours or less when administered orally.

This wherein clause was relevant when claim 1 encompassed unspecified direct factor Xa inhibitors. However, the claim was amended and now recites one specific direct factor Xa inhibitor, rivaroxaban. For rivaroxaban, a plasma concentration half life of 4-6 hours has been demonstrated at steady state in human. Specification, p. 4 line 6-9, citing Kubitza[1] (D. Kubitza et al., Multiple Dose Escalation Study Investigating the Pharmacokinetics, Safety, and Pharmacokinetics of Bayer 59-7939 an Oral, Direct Factor Xa Inhibitor in Healthy Male Subjects, Blood 2003, 102, Abstract 3004). Because the plasma concentration half-life limitation is inherent to rivaroxaban, the wherein clause is redundant and is not needed.

Claims 1, 4, 5, 11 and 18 are currently under examination.

Double Patenting

The Patent Office rejects claims 1, 4, 5, 11 and 18 for double patenting over claims 13, 24 and 30 of US Patent 7,157,456. The Patent Office also rejects claims 1, 4, 5, 11 and 18 for double patenting over claims 1-6 and 17-21 of US Patent 7,592,339. Yet the patented claims only disclose rivaroxaban and its use to treat and prevent thromboembolic disorders. These patented claims do not disclose (1) a once daily treatment of rivaroxaban (2) for at least five days (3) in a rapid-release oral dosage form. Because the patented claims do not mention these parameters, they cannot be found to suggest that such a therapy would be medically effective. For this reason, Applicants respectfully submit that the patented claims do not render obvious the present claims. Thus, the present claims are patentably distinct from the patented claims.

Additionally, Applicants refer to the discussion below concerning obviousness and obviousness-type double patenting. That discussion further explains why the claimed once daily dosaging was not obvious, and therefore why it is patentably distinct from the claims of the '456 and '339 patents.

For these reasons, reconsideration and withdrawal of the double patenting rejection is urged.

Obviousness-type Double Patenting/ Obviousness Rejections

Claims 1, 4, 5, 11 and 18 stand rejected under two legal grounds that rely on combinations of very similar references.

For obviousness-type double patenting, the Office Action refers to the claims mentioned above in the '456 and '339 patents and combines them with Kubitza[1] (D. Kubitza et al., Multiple Dose Escalation Study Investigating the Pharmacokinetics, Safety, and Pharmacokinetics of Bayer 59-7939 an Oral, Direct Factor Xa Inhibitor in Healthy Male Subjects, Blood 2003, 102, Abstract 3004) and Kubitza[2] (Single Dose Escalation Study Investigating the Pharmacodynamics, Safety, and Pharmacokinetics of BAY 59-7939 an Oral, Direct Factor Xa Inhibitor in Healthy Male Subjects, abstract 2010, Blood, vol. 102:11, 16 November, 2003, p. 813).

For obviousness, the Office Action refers to Straub et al. (US 2003/0156310 A1) in view of Kubitza[1] and Kubitza[2].

Both the '456 and '339 patents and the Straub et al. patent application are relied upon for disclosing rivaroxaban to treat thromboembolic disorders.

For each rejection, the Office relies upon Kubitza[1] and Kubitza[2] as teaching or suggesting once daily dosing with a rapid release over five days. The Office found a reasonable expectation of success from this modification of the Straub et al. patent teachings in the Kubitza articles teachings that their dosages were safe and tolerable. Office Action, p. 11.

Applicants respectfully disagree.

The art of developing a safe and efficacious dosage regimen for a drug involves many steps after a molecule is identified as having biological activity. In the initial human trials, the drug is tested in healthy human volunteers. The first human tests identify the safety and the pharmacokinetic (PK) and pharmacodynamic (PD) properties of the drug. The drug is not initially tested in sick patients because it is better to test in healthy volunteers with no known risk factors for disease who are at the least risk of being harmed by a wrong dose. Furthermore, one cannot start dosage trials of an anticoagulant in ill patients that require an anticoagulant. Such patients cannot be treated ethically with a drug at a dosage that has not been shown to work or at too high of a dose that may cause an unacceptable degree of bleeding, and they cannot be used in a trial with a placebo. Thus, patients requiring an anticoagulant cannot be the first line for testing dosages of a new anticoagulant.

Kubitza[1] and Kubitza[2] report the results of some of the very first rivaroxaban dosage testing in humans. Both abstracts report tests in healthy human volunteers (see the abstract titles). Kubitza[2] reports the results of administering a single dose only of rivaroxaban to healthy volunteers. Each volunteer only received one dose, and the dosages varied among the different volunteers. Kubitza[1] reports a multiple dose escalation study in healthy human volunteers in which six different dosage regimens were tested, each for five days. Only one of these dosing regimens involved a once daily dosage, and that was in the lowest overall dosage amount (5 mg)

tested. See Kubitza[1], line 4 discussing dosages of 5 mg od, bid, or tid and 10 mg, 20 mg, or 30 mg bid for five days.

However, neither Kubitza[1] nor Kubitza[2] discusses what dosage would be efficacious. Indeed, they cannot teach efficacious dosages because they report results in healthy patients who are not at a heightened risk for thromboembolism. From healthy volunteers, the general safety of the drug can be determined. Also, the PK and PD parameters can be measured, which differentiate the types of dosage trials to use in later studies. However, with healthy volunteers as in the cited Kubitza abstracts, one of ordinary skill in the art cannot determine the efficacy of a dose.

The final Office Action asserted that because the specification defines "treatment" to include prophylactic treatment of thromboembolic disorders, the patient population includes healthy subjects because anyone could be at risk of thromboembolism. Office Action, pp. 4-5. Applicants respectfully disagree.

The claims recite treating a patient "in need thereof" and such patients are well understood in the medical field to be at a significantly increased risk of thromboembolism. For example, prophylaxis with rivaroxaban is advised for patients undergoing hip or knee replacements, which involve a stopping of blood flow in a particular extremity that allows the opportunity for blood to pool and therefore to coagulate. A healthy volunteer such as those in the Kubitza[1] and Kubitza[2] studies is not undergoing hip or knee replacement and does not have this increased coagulation risk. Also, rivaroxaban is indicated for reducing the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. See attached Xarelto® rivaroxaban prescribing information (November 2011). This condition also involves an increased risk of blood pooling and therefore of thromboembolisms. These indications are just two examples of the many prophylactic uses possible for rivaroxaban. They show that prophylaxis for thromboembolism in a patient in need thereof involves a patient at a heightened risk for thromboembolism and not the healthy volunteers as in the Kubitza[1] and Kubitza[2] abstracts.

Maintenance of normal haemostasis – the balance between bleeding and thrombosis – is subject to complex regulatory mechanisms. Specification, page 1 lines 19-20. Administration of an anticoagulant involves balancing between the increased need for coagulation in the ill patient and the increased risk of bleeding from the anticoagulant. One of ordinary skill in the art does not distort the normal homeostasis in a healthy person by administering an anticoagulant.

For this reason, the Patent Office's assumption that healthy people would be within the patient population of the present claim is incorrect. The claims recite administration for "treating a thromboembolic disorder" in "a patient in need thereof." One of ordinary skill would understand that treatment of a thromboembolic disorder – even including prophylaxis - is only for a person with increased risk of thromboembolism. Thus, the Kubitza abstracts do not disclose treatment of persons within the scope of the present claims.

Furthermore, both abstracts report a half life for rivaroxaban that would lead the ordinary artisan to expect that multiple daily dosages would be required. When a drug substance is applied in no more than a therapeutically effective amount, which is usually preferred to minimize the exposure of patients and avoid side effects, the drug must be given approximately every half life. See specification at page 3 lines 4-8, citing Malcolm Rowland and Thomas Tozer, "Clinical Pharmacokinetics," 1995, pp.83. Both Kubitza[1] and Kubitza[2] report half lives for rivaroxaban that would indicate multiple daily dosages were required: a half life of 4-6 hours (Kubitza[2]) or 3-4 hours (Kubitza[1]).

The Office Action also supposes that the skilled person would have been motivated to administer rivaroxaban once daily using the rapid release tablet of Kubitza[2] for patient convenience and compliance. Office Action, p. 11. Again, Applicants disagree. The ordinary skilled person would have read Kubitza[2] as reporting early tests of a ***single administration*** of rivaroxaban to 103 healthy volunteers in order to test safety, PK and PD across a very broad range of dosage amounts. This ordinary person would not have found any teaching from Kubitza[1] of what dosage would be efficacious, let alone that an efficacious dosage could be a once daily dosage in a rapid release dosage form over at least five days.

The Office Action also supposes that the ordinary skilled person would have had a reasonable expectation of successfully treating deep vein thrombosis by administering rivaroxaban once daily in a rapid release dosage form because Kubitza[1] and Kubitza[2] teach administration guidelines for rivaroxaban that are safe and tolerable for patients. Office Action, p. 11. Although admittedly both abstracts report that rivaroxaban was safe and well tolerated, this was in healthy volunteers rather than ill patients, and neither abstract suggests what dosage would be efficacious in preventing deep vein thrombosis or treating thromboembolisms generally in a person at heightened risk.

For these reasons, Applicants respectfully submit that the Office's conclusions of obviousness and of obviousness-type double patenting are not well grounded and respectfully request that the rejections be reconsidered and withdrawn.

Response to Arguments

The final Office Action asked for clarification of Applicants' previous remarks concerning the k_i value for free factor Xa, its free plasma concentration, and the free plasma concentrations of rivaroxaban, and mentioning an elimination half life of 11-13 hours. Office Action, pages 5-6. Applicants clarify that this was the explanation determined after the application was filed for why rivaroxaban could be dosed efficaciously only once a day in a rapid release dosage form.

This explanation in the prior response referred to a half life of 11-13 hours. This is the half life in elderly patients, which is a significant group of the patients that receive rivaroxaban. The half life in elderly patients is different than the half life reported in the present application and in Kubitza[1] and Kubitza[2] that involved calculations from a broader patient age group. See attached Xarelto® prescribing information, page 6 right col. for discussion of the half life in elderly patients. Applicants' discussion in its prior response at pages 6-7 was not to show unexpectedly superior results but rather to show why rivaroxaban worked with once daily dosaging of a rapid release dosage form when the presumption based on half life was that such dosaging would not work effectively.

The final Office Action also discusses the data Applicants referred to in table 1-1 that shows that once daily dosaging of 30 mg is in line with results from twice daily 30 mg dosaging. The Office then states that the total dosage is not the same between the two, and states that the 20 mg bid (40 mg total) appears to be the most effective. Office Action, pp. 6-7. Indeed, Applicants agree that efficacy results were better with 20 mg bid than with 30 mg od as shown in table 1-1. However, the data in tables 1-1 and 1-2 shows that the results for both efficacy and major bleeding events for 30 mg od fall between 20 mg and 40 mg total dosages, each of which were administered bid. From this, the inventors concluded ***that once daily dosaging*** of rivaroxaban with a rapid release formulation to treat thromboembolism ***was possible***. In sum, the data in tables 1-1 and 1-2 is not relied upon to show that once daily dosaging was surprisingly superior to the other dosages tested, but rather that its efficacy fell where one would have expected a bid dosage to be and its side effects (bleeding) also fell where a bid dosage was expected to be. Thus, the data shows that once daily dosaging with a rapid release dosage form was possible.

As the Patent Office clearly agrees, once daily dosaging is very advantageous for the patient to ease administration and to improve patient compliance. The fact that rivaroxaban may be administered efficaciously once daily in a rapid release dosage form allows this patient benefit to be obtained, which was not expected from the half life data on rivaroxaban.

Information Disclosure Statement (IDS)

In the final Office Action, certain references contained on the June 17, 2011 IDS were not considered. The Office stated that these references were not considered because English language translations were not provided and their relevance to the application had not been indicated.

Applicants respectfully disagree. On pages 2 and 3 of the Information Disclosure Statement accompanying the PTO Form SB08, Applicants provided detailed statements of the content of these foreign-language documents and in one case referred to pages of the specification where the reference was discussed. This satisfies the standards of Rule 98, which is as follows (emphasis added):

37 CFR 1.98 (a) (3) (i):

> A ***concise explanation of the relevance***, as it is presently understood by the individual designated in § **1.56**(c) most knowledgeable about the content of the information, of each patent, publication, or other information listed that is not in the English language. The concise explanation may be either separate from applicant's specification or incorporated therein.

Accordingly, reconsideration of the IDS and initialing of the foreign language references is respectfully requested.

CONCLUSION

In view of the above remarks and amendments, Applicants respectfully request withdrawal of the rejections and allowance of the claims. If any outstanding issues remain, the Examiner is invited to telephone the undersigned at the number given below.

Applicants reserve all rights to pursue the non-elected claims and subject matter in one or more divisional applications.

This response is filed with a petition for two-month extension of time and authorization to charge the fee required to the undersigned's credit card. No additional fee is believed due. However, if an additional fee is due, the Director is hereby authorized to charge our Deposit Account No. 03-2775, under Order No. 11987-00042-US from which the undersigned is authorized to draw.

Dated: January 30, 2012

Respectfully submitted,

Christine Hansen

#4,488,478

Christine M. Hansen
Registration No.: 40,634
CONNOLLY BOVE LODGE & HUTZ LLP
1007 North Orange Street
P. O. Box 2207
Wilmington, Delaware 19899-2207
(302) 658-9141
Attorney for Applicant

XARELTO®
(rivaroxaban) tablets, for oral use

Issued: November 2011
02X11309A

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use XARELTO® (rivaroxaban) safely and effectively. See full prescribing information for XARELTO.

XARELTO (rivaroxaban) tablets, for oral use
Initial U.S. Approval: 2011

WARNINGS: (A) DISCONTINUING XARELTO IN PATIENTS WITH NONVALVULAR ATRIAL FIBRILLATION INCREASES RISK OF STROKE, (B) SPINAL/EPIDURAL HEMATOMA
See full prescribing information for complete boxed warning

A. DISCONTINUING XARELTO IN PATIENTS WITH NONVALVULAR ATRIAL FIBRILLATION

Discontinuing XARELTO places patients at an increased risk of thrombotic events. If anticoagulation with XARELTO must be discontinued for a reason other than pathological bleeding, consider administering another anticoagulant (2.1, 5.1, 14.1).

B. SPINAL/EPIDURAL HEMATOMA

Epidural or spinal hematomas have occurred in patients treated with XARELTO who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis (5.2, 5.3, 6.2).

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary (5.3).

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis (5.3).

----------RECENT MAJOR CHANGES----------

Boxed Warning	11/2011
Indications and Usage (1.1)	11/2011
Dosage and Administration (2.1, 2.3)	11/2011
Contraindications (4)	11/2011
Warnings and Precautions (5.1, 5.2, 5.5)	11/2011

----------INDICATIONS AND USAGE----------

XARELTO is a factor Xa inhibitor indicated:
- to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (1.1)
- for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE) in patients undergoing knee or hip replacement surgery (1.2)

----------DOSAGE AND ADMINISTRATION----------

- Nonvalvular Atrial Fibrillation:
  - o For patients with CrCl >50 mL/min: 20 mg orally, once daily **with the evening meal** (2.1)
  - o For patients with CrCl 15 - 50 mL/min: 15 mg orally, once daily **with the evening meal** (2.1)
  - o Avoid use in patients with CrCl <15 mL/min (2.3)
- Prophylaxis of DVT: 10 mg orally, once daily with or without food (2.2)
- Hepatic impairment (for nonvalvular AF and prophylaxis of DVT indications):
  - o Avoid use in patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment or with any degree of hepatic disease associated with coagulopathy (2.3, 8.8).

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 10 mg, 15 mg, and 20 mg (3)

----------CONTRAINDICATIONS----------

- Active pathological bleeding (4)
- Severe hypersensitivity reaction to XARELTO (4)

----------WARNINGS AND PRECAUTIONS----------

- Risk of bleeding: XARELTO can cause serious and fatal bleeding. Promptly evaluate signs and symptoms of blood loss. (5.2)
- Pregnancy related hemorrhage: Use XARELTO with caution in pregnant women due to the potential for obstetric hemorrhage and/or emergent delivery. Promptly evaluate signs and symptoms of blood loss. (5.4)

----------ADVERSE REACTIONS----------

The most common adverse reaction (>5%) was bleeding. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Pharmaceuticals, Inc. at 1-800-526-7736 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

- Combined P-gp and strong CYP3A4 inhibitors and inducers: Avoid concomitant use (7.1, 7.2)
- Prophylaxis of DVT:
  - o Anticoagulants: Avoid concomitant use (7.3)

----------USE IN SPECIFIC POPULATIONS----------

- Nursing mothers: discontinue drug or discontinue nursing (8.3)
- Renal impairment:
  - o Prophylaxis of DVT: Avoid use in patients with severe impairment (CrCl <30 mL/min). Use with caution in moderate impairment (CrCl 30 to <50 mL/min) (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 11/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNINGS: (A) DISCONTINUING XARELTO IN PATIENTS WITH NONVALVULAR ATRIAL FIBRILLATION INCREASES RISK OF STROKE, (B) SPINAL/EPIDURAL HEMATOMA

A. DISCONTINUING XARELTO IN PATIENTS WITH NONVALVULAR ATRIAL FIBRILLATION

Discontinuing XARELTO places patients at an increased risk of thrombotic events. An increased rate of stroke was observed following XARELTO discontinuation in clinical trials in atrial fibrillation patients. If anticoagulation with XARELTO must be discontinued for a reason other than pathological bleeding, consider administering another anticoagulant *[see Dosage and Administration (2.1), Warnings and Precautions (5.1), and Clinical Studies (14.1)]*.

B. SPINAL/EPIDURAL HEMATOMA

Epidural or spinal hematomas have occurred in patients treated with XARELTO who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:

- **use of indwelling epidural catheters**
- **concomitant use of other drugs that affect hemostasis, such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants**
- **a history of traumatic or repeated epidural or spinal punctures**
- **a history of spinal deformity or spinal surgery**

***[see Warnings and Precautions (5.2, 5.3) and Adverse Reactions (6.2)]*.**

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary *[see Warnings and Precautions (5.3)]*.

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis *[see Warnings and Precautions (5.3)]*.

1 INDICATIONS AND USAGE

1.1 Reduction of Risk of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation

XARELTO (rivaroxaban) is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

There are limited data on the relative effectiveness of XARELTO and warfarin in reducing the risk of stroke and systemic embolism when warfarin therapy is well-controlled *[see Clinical Studies (14.1)]*.

1.2 Prophylaxis of Deep Vein Thrombosis

XARELTO (rivaroxaban) is indicated for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE) in patients undergoing knee or hip replacement surgery.

2 DOSAGE AND ADMINISTRATION

2.1 Nonvalvular Atrial Fibrillation

For patients with creatinine clearance (CrCl) >50 mL/min, the recommended dose of XARELTO is 20 mg taken orally once daily with the evening meal. For patients with CrCl 15 to 50 mL/min, the recommended dose is 15 mg once daily with the evening meal *[see Use in Specific Populations (8.7)]*.

Switching from or to Warfarin - When switching patients from warfarin to XARELTO, discontinue warfarin and start XARELTO as soon as the International Normalized Ratio (INR) is below 3.0 to avoid periods of inadequate anticoagulation.

No clinical trial data are available to guide converting patients from XARELTO to warfarin. XARELTO affects INR, so INR measurements made during co-administration with warfarin may not be useful for determining the appropriate dose of warfarin. One approach is to discontinue XARELTO and begin both a parenteral anticoagulant and warfarin at the time the next dose of XARELTO would have been taken.

Switching from or to Anticoagulants other than Warfarin - For patients currently receiving an anticoagulant other than warfarin, start XARELTO 0 to 2 hours prior to the next scheduled evening administration of the drug (e.g., low molecular weight heparin or non-warfarin oral anticoagulant) and omit administration of the other anticoagulant. For unfractionated heparin being administered by continuous infusion, stop the infusion and start XARELTO at the same time.

For patients currently taking XARELTO and transitioning to an anticoagulant with rapid onset, discontinue XARELTO and give the first dose of the other anticoagulant (oral or parenteral) at the time that the next XARELTO dose would have been taken *[see Drug Interactions (7.3)]*.

2.2 Prophylaxis of Deep Vein Thrombosis

The recommended dose of XARELTO is 10 mg taken orally once daily with or without food. The initial dose should be taken at least 6 to 10 hours after surgery once hemostasis has been established.

- For patients undergoing hip replacement surgery, treatment duration of 35 days is recommended.
- For patients undergoing knee replacement surgery, treatment duration of 12 days is recommended.

XARELTO® (rivaroxaban) tablets

2.3 General Dosing Instructions

Hepatic Impairment

No clinical data are available for patients with severe hepatic impairment. Avoid use of XARELTO in patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment or with any hepatic disease associated with coagulopathy *[see Use in Specific Populations (8.8)]*.

Renal Impairment

Nonvalvular Atrial Fibrillation

Avoid the use of XARELTO in patients with CrCl <15 mL/min. Periodically assess renal function as clinically indicated (i.e., more frequently in situations in which renal function may decline) and adjust therapy accordingly. Discontinue XARELTO in patients who develop acute renal failure while on XARELTO *[see Use in Specific Populations (8.7)]*.

Prophylaxis of Deep Vein Thrombosis

Avoid the use of XARELTO in patients with severe renal impairment (CrCl <30 mL/min) due to an expected increase in rivaroxaban exposure and pharmacodynamic effects in this patient population. Observe closely and promptly evaluate any signs or symptoms of blood loss in patients with moderate renal impairment (CrCl 30 to 50 mL/min). Patients who develop acute renal failure while on XARELTO should discontinue the treatment *[see Use in Specific Populations (8.7)]*.

Surgery and Intervention

If anticoagulation must be discontinued to reduce the risk of bleeding with surgical or other procedures, XARELTO should be stopped at least 24 hours before the procedure. In deciding whether a procedure should be delayed until 24 hours after the last dose of XARELTO, the increased risk of bleeding should be weighed against the urgency of intervention. XARELTO should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established. If oral medication cannot be taken after surgical intervention, consider administering a parenteral anticoagulant.

Missed Dose

If a dose of XARELTO is not taken at the scheduled time, administer the dose as soon as possible on the same day.

Use with P-gp and Strong CYP3A4 Inhibitors or Inducers

Avoid concomitant use of XARELTO with combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir/ritonavir, and conivaptan) *[see Drug Interactions (7.1)]*.

Avoid concomitant use of XARELTO with drugs that are combined P-gp and strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, St. John's wort) *[see Drug Interactions (7.2)]*.

3 DOSAGE FORMS AND STRENGTHS

- 10 mg tablets: Round, light red, biconvex and film-coated with a triangle pointing down above a "10" marked on one side and "Xa" on the other side
- 15 mg tablets: Round, red, biconvex, and film-coated with a triangle pointing down above a "15" marked on one side and "Xa" on the other side
- 20 mg tablets: Triangle-shaped, dark red, and film-coated with a triangle pointing down above a "20" marked on one side and "Xa" on the other side

4 CONTRAINDICATIONS

XARELTO is contraindicated in patients with:

- active pathological bleeding *[see Warnings and Precautions (5.2)]*
- severe hypersensitivity reaction to XARELTO *[see Warnings and Precautions (5.5)]*

5 WARNINGS AND PRECAUTIONS

5.1 Increased Risk of Stroke after Discontinuation in Nonvalvular Atrial Fibrillation

Discontinuing XARELTO in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from XARELTO to warfarin in clinical trials in atrial fibrillation patients. If XARELTO must be discontinued for a reason other than pathological bleeding, consider administering another anticoagulant *[see Dosage and Administration (2.1) and Clinical Studies (14.1)]*.

5.2 Risk of Bleeding

XARELTO increases the risk of bleeding and can cause serious or fatal bleeding. In deciding whether to prescribe XARELTO to patients at increased risk of bleeding, the risk of thrombotic events should be weighed against the risk of bleeding.

Promptly evaluate any signs or symptoms of blood loss. Discontinue XARELTO in patients with active pathological hemorrhage.

A specific antidote for rivaroxaban is not available. Because of high plasma protein binding, rivaroxaban is not expected to be dialyzable *[see Clinical Pharmacology (12.3)]*. Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban. There is no experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving rivaroxaban. There is neither scientific rationale for benefit nor experience with systemic hemostatics (desmopressin and aprotinin) in

individuals receiving rivaroxaban. Use of procoagulant reversal agents such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC), or recombinant factor VIIa (rFVIIa) may be considered, but has not been evaluated in clinical trials.

Concomitant use of drugs affecting hemostasis increases the risk of bleeding. These include aspirin, $P2Y_{12}$ platelet inhibitors, other antithrombotic agents, fibrinolytic therapy, and non-steroidal anti-inflammatory drugs (NSAIDs) *[see Drug Interactions (7.3), (7.4), (7.5)]*.

Concomitant use of drugs that are combined P-gp and CYP3A4 inhibitors (e.g. ketoconazole and ritonavir) increases rivaroxaban exposure and may increase bleeding risk *[see Drug Interactions (7.1)]*.

5.3 Spinal/Epidural Anesthesia or Puncture

When neuraxial anesthesia (spinal/epidural anesthesia) or spinal puncture is employed, patients treated with anticoagulant agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis *[see Boxed Warning]*.

An epidural catheter should not be removed earlier than 18 hours after the last administration of XARELTO. The next XARELTO dose is not to be administered earlier than 6 hours after the removal of the catheter. If traumatic puncture occurs, the administration of XARELTO is to be delayed for 24 hours.

5.4 Risk of Pregnancy Related Hemorrhage

XARELTO should be used with caution in pregnant women and only if the potential benefit justifies the potential risk to the mother and fetus. XARELTO dosing in pregnancy has not been studied. The anticoagulant effect of XARELTO cannot be monitored with standard laboratory testing nor readily reversed. Promptly evaluate any signs or symptoms suggesting blood loss (e.g., a drop in hemoglobin and/or hematocrit, hypotension, or fetal distress).

5.5 Severe Hypersensitivity Reactions

There were postmarketing cases of anaphylaxis in patients treated with XARELTO to reduce the risk of DVT. Patients who have a history of a severe hypersensitivity reaction to XARELTO should not receive XARELTO *[see Adverse Reactions (6.2)]*.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

During clinical development for the approved indications, 11598 patients were exposed to XARELTO. These included 7111 patients who received XARELTO 15 mg or 20 mg orally once daily for a mean of 19 months (5558 for 12 months and 2512 for 24 months) to reduce the risk of stroke and systemic embolism in nonvalvular atrial fibrillation (ROCKET AF) and 4487 patients who received XARELTO 10 mg orally once daily for prophylaxis of DVT following hip or knee replacement surgery (RECORD 1-3).

Hemorrhage

The most common adverse reactions with XARELTO were bleeding complications *[see Warnings and Precautions (5.2)]*.

Nonvalvular Atrial Fibrillation

In the ROCKET AF trial, the most frequent adverse reactions associated with permanent drug discontinuation were bleeding events, with incidence rates of 4.3% for XARELTO vs. 3.1% for warfarin. The incidence of discontinuations for non-bleeding adverse events was similar in both treatment groups.

Table 1 shows the number of patients experiencing various types of bleeding events in the ROCKET AF study.

Table 1: Bleeding Events in ROCKET AF*

Parameter	XARELTO N = 7111 n (%)	Event Rate (per 100 Pt-yrs)	Warfarin N = 7125 n (%)	Event Rate (per 100 Pt-yrs)
Major bleeding†	395 (5.6)	3.6	386 (5.4)	3.5
Bleeding into a critical organ‡	91 (1.3)	0.8	133 (1.9)	1.2
Fatal bleeding	27 (0.4)	0.2	55 (0.8)	0.5
Bleeding resulting in transfusion of ≥ 2 units of whole blood or packed red blood cells	183 (2.6)	1.7	149 (2.1)	1.3
Gastrointestinal bleeding	221 (3.1)	2.0	140 (2.0)	1.2

*For all sub-types of major bleeding, single events may be represented in more than one row, and individual patients may have more than one event.

XARELTO® (rivaroxaban) tablets

† Defined as clinically overt bleeding associated with a decrease in hemoglobin of ≥ 2 g/dL, transfusion of ≥ 2 units of packed red blood cells or whole blood, bleeding at a critical site, or with a fatal outcome. Hemorrhagic strokes are counted as both bleeding and efficacy events. Major bleeding rates excluding strokes are 3.3 per 100 Pt-yrs for XARELTO vs. 2.9 per 100 Pt-yrs for warfarin.

‡ The majority of the events were intracranial, and also included intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome, or retroperitoneal.

Prophylaxis of Deep Vein Thrombosis

In the RECORD clinical trials, the overall incidence rate of adverse reactions leading to permanent treatment discontinuation was 3.7% with XARELTO.

The mean duration of XARELTO treatment was 11.9 days in the total knee replacement study and 33.4 days in the total hip replacement studies. Overall, in the RECORD program, the mean age of the patients studied in the XARELTO group was 64 years, 59% were female and 82% were Caucasian. Twenty-seven percent (1206) of patients underwent knee replacement surgery and 73% (3281) underwent hip replacement surgery.

The rates of major bleeding events and any bleeding events observed in patients in the RECORD clinical trials are shown in Table 2.

Table 2: Bleeding Events* in Patients Undergoing Hip or Knee Replacement Surgeries (RECORD 1-3)

	XARELTO 10 mg	Enoxaparin†
Total treated patients	**N = 4487 n (%)**	**N = 4524 n (%)**
Major bleeding event	14 (0.3)	9 (0.2)
Fatal bleeding	1 (<0.1)	0
Bleeding into a critical organ	2 (<0.1)	3 (0.1)
Bleeding that required re-operation	7 (0.2)	5 (0.1)
Extra-surgical site bleeding requiring transfusion of >2 units of whole blood or packed cells	4 (0.1)	1 (<0.1)
Any bleeding event‡	261 (5.8)	251 (5.6)
Hip Surgery Studies	**N = 3281 n (%)**	**N = 3298 n (%)**
Major bleeding event	7 (0.2)	3 (0.1)
Fatal bleeding	1 (<0.1)	0
Bleeding into a critical organ	1 (<0.1)	1 (<0.1)
Bleeding that required re-operation	2 (0.1)	1 (<0.1)
Extra-surgical site bleeding requiring transfusion of >2 units of whole blood or packed cells	3 (0.1)	1 (<0.1)
Any bleeding event‡	201 (6.1)	191 (5.8)
Knee Surgery Study	**N = 1206 n (%)**	**N = 1226 n (%)**
Major bleeding event	7 (0.6)	6 (0.5)
Fatal bleeding	0	0
Bleeding into a critical organ	1 (0.1)	2 (0.2)
Bleeding that required re-operation	5 (0.4)	4 (0.3)
Extra-surgical site bleeding requiring transfusion of >2 units of whole blood or packed cells	1 (0.1)	0
Any bleeding event‡	60 (5.0)	60 (4.9)

* Bleeding events occurring any time following the first dose of double-blind study medication (which may have been prior to administration of active drug) until two days after the last dose of double-blind study medication. Patients may have more than one event.

† Includes the placebo-controlled period for RECORD 2, enoxaparin dosing was 40 mg once daily (RECORD 1-3)

‡ Includes major bleeding events

Following XARELTO treatment, the majority of major bleeding complications (≥60%) occurred during the first week after surgery.

Other Adverse Reactions

Non-hemorrhagic adverse drug reactions (ADRs) reported in ≥1% of XARELTO-treated patients are shown in Table 3.

Table 3: Other Adverse Drug Reactions* Reported by ≥1% of XARELTO-Treated Patients in RECORD 1-3 Studies

System/Organ Class Adverse Reaction	XARELTO 10 mg (N = 4487) n (%)	Enoxaparin† (N = 4524) n (%)
Injury, poisoning and procedural complications		
Wound secretion	125 (2.8)	89 (2.0)
Musculoskeletal and connective tissue disorders		
Pain in extremity	74 (1.7)	55 (1.2)
Muscle spasm	52 (1.2)	32 (0.7)
Nervous system disorders		
Syncope	55 (1.2)	32 (0.7)
Skin and subcutaneous tissue disorders		
Pruritus	96 (2.1)	79 (1.8)
Blister	63 (1.4)	40 (0.9)

* ADR occurring any time following the first dose of double-blind medication, which may have been prior to administration of active drug, until two days after the last dose of double-blind study medication.

† Includes the placebo-controlled period of RECORD 2, enoxaparin dosing was 40 mg once daily (RECORD 1-3)

Other clinical trial experience: In an investigational study of acute medically ill patients being treated with XARELTO 10 mg tablets, cases of pulmonary hemorrhage and pulmonary hemorrhage with bronchiectasis were observed.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of rivaroxaban. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and lymphatic system disorders: agranulocytosis

Gastrointestinal disorders: retroperitoneal hemorrhage

Hepatobiliary disorders: jaundice, cholestasis, cytolytic hepatitis

Immune system disorders: hypersensitivity, anaphylactic reaction, anaphylactic shock

Nervous system disorders: cerebral hemorrhage, subdural hematoma, epidural hematoma, hemiparesis

Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome

7 DRUG INTERACTIONS

Rivaroxaban is a substrate of CYP3A4/5, CYP2J2, and the P-gp and ATP-binding cassette G2 (ABCG2) transporters. Inhibitors and inducers of these CYP450 enzymes or transporters (e.g., P-gp) may result in changes in rivaroxaban exposure.

7.1 Drugs that Inhibit Cytochrome P450 3A4 Enzymes and Drug Transport Systems

In drug interaction studies evaluating the concomitant use with drugs that are combined P-gp and CYP3A4 inhibitors, increases in rivaroxaban exposure and pharmacodynamic effects (i.e., factor Xa inhibition and PT prolongation) were observed. Significant increases in rivaroxaban exposure may increase bleeding risk.

- *Ketoconazole (combined P-gp and strong CYP3A4 inhibitor):* Steady-state rivaroxaban AUC and C_{max} increased by 160% and 70%, respectively. Similar increases in pharmacodynamic effects were also observed.
- *Ritonavir (combined P-gp and strong CYP3A4 inhibitor):* Single-dose rivaroxaban AUC and C_{max} increased by 150% and 60%, respectively. Similar increases in pharmacodynamic effects were also observed.
- *Clarithromycin (combined P-gp and strong CYP3A4 inhibitor):* Single-dose rivaroxaban AUC and C_{max} increased by 50% and 40%, respectively. The smaller increases in exposure observed for clarithromycin compared to ketoconazole or ritonavir may be due to the relative difference in P-gp inhibition.
- *Erythromycin (combined P-gp and moderate CYP3A4 inhibitor):* Both the single-dose rivaroxaban AUC and C_{max} increased by 30%.
- *Fluconazole (moderate CYP3A4 inhibitor):* Single-dose rivaroxaban AUC and C_{max} increased by 40% and 30%, respectively.

Avoid concomitant administration of XARELTO with combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir/ritonavir, and conivaptan), which cause significant increases in rivaroxaban exposure that may increase bleeding risk.

Prophylaxis of Deep Vein Thrombosis

When clinical data suggest a change in exposure is unlikely to affect bleeding risk (e.g., clarithromycin, erythromycin), no precautions are necessary during coadministration with drugs that are combined P-gp and CYP3A4 inhibitors.

7.2 Drugs that Induce Cytochrome P450 3A4 Enzymes and Drug Transport Systems

In a drug interaction study, co-administration of XARELTO (20 mg single dose with food) with a drug that is a combined P-gp and strong CYP3A4 inducer (rifampicin titrated up to 600 mg once daily) led to an approximate decrease of 50% and 22% in AUC and C_{max}, respectively. Similar decreases in pharmacodynamic effects were also observed. These decreases in exposure to rivaroxaban may decrease efficacy.

Avoid concomitant use of XARELTO with drugs that are combined P-gp and strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, St. John's wort).

7.3 Anticoagulants

In a drug interaction study, single doses of enoxaparin (40 mg subcutaneous) and XARELTO (10 mg) given concomitantly resulted in an additive effect on anti-factor Xa activity. Enoxaparin did not affect the pharmacokinetics of rivaroxaban. In another study, single doses of warfarin (15 mg) and XARELTO (5 mg) resulted in an additive effect on factor Xa inhibition and PT. Warfarin did not affect the pharmacokinetics of rivaroxaban.

Prophylaxis of Deep Vein Thrombosis

Avoid concurrent use of XARELTO with other anticoagulants due to the increased bleeding risk. Promptly evaluate any signs or symptoms of blood loss *[see Warnings and Precautions (5.2)]*.

7.4 NSAIDs/Aspirin

In ROCKET AF, concomitant aspirin use (almost exclusively at a dose of 100 mg or less) during the double-blind phase was identified as an independent risk factor for major bleeding. NSAIDs are known to increase bleeding, and bleeding risk may be increased when NSAIDs are used concomitantly with XARELTO. In a single-dose drug interaction study there were no pharmacokinetic or pharmacodynamic interactions observed after concomitant administration of naproxen or aspirin (acetylsalicylic acid) with XARELTO.

Promptly evaluate any signs or symptoms of blood loss if patients are treated concomitantly with aspirin, other platelet aggregation inhibitors, or NSAIDs *[see Warnings and Precautions (5.2)]*.

7.5 Clopidogrel

In two drug interaction studies where clopidogrel (300 mg loading dose followed by 75 mg daily maintenance dose) and XARELTO (15 mg single dose) were co-administered in healthy subjects, an increase in bleeding time to 45 minutes was observed in approximately 45% and 30% of subjects in these studies, respectively. The change in bleeding time was approximately twice the maximum increase seen with either drug alone. There was no change in the pharmacokinetics of either drug.

Promptly evaluate any signs or symptoms of blood loss if patients are treated concomitantly with clopidogrel *[see Warnings and Precautions (5.2)]*.

7.6 Drug-Disease Interactions with Drugs that Inhibit Cytochrome P450 3A4 Enzymes and Drug Transport Systems

Based on simulated pharmacokinetic data, patients with renal impairment receiving full dose XARELTO in combination with drugs classified as combined P-gp and weak or moderate CYP3A4 inhibitors (e.g., amiodarone, diltiazem, verapamil, quinidine, ranolazine, dronedarone, felodipine, erythromycin, and azithromycin) may have significant increases in exposure compared with patients with normal renal function and no inhibitor use, since both pathways of rivaroxaban elimination are affected.

While increases in rivaroxaban exposure can be expected under such conditions, results from an analysis in the ROCKET AF trial, which allowed concomitant use with combined P-gp and weak or moderate CYP3A4 inhibitors (e.g., amiodarone, diltiazem, verapamil, chloramphenicol, cimetidine, and erythromycin), did not show an increase in bleeding in patients with CrCl 30 to <50 mL/min [Hazard Ratio (95% CI): 1.05 (0.77, 1.42)]. XARELTO should be used in patients with CrCL 15 to 50 mL/min who are receiving concomitant combined P-gp and weak or moderate CYP3A4 inhibitors only if the potential benefit justifies the potential risk *[see Use in Specific Populations (8.7)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate or well-controlled studies of XARELTO in pregnant women, and dosing for pregnant women has not been established. Use XARELTO with caution in pregnant patients because of the potential for pregnancy related hemorrhage and/or emergent delivery with an anticoagulant that is not readily reversible. The anticoagulant effect of XARELTO cannot be reliably monitored with standard laboratory testing. Animal reproduction studies showed no increased risk of structural malformations, but increased post-implantation

pregnancy loss occurred in rabbits. XARELTO should be used during pregnancy only if the potential benefit justifies the potential risk to mother and fetus *[see Warnings and Precautions (5.4)]*.

Rivaroxaban crosses the placenta in animals. Animal reproduction studies have shown pronounced maternal hemorrhagic complications in rats and an increased incidence of post-implantation pregnancy loss in rabbits. Rivaroxaban increased fetal toxicity (increased resorptions, decreased number of live fetuses, and decreased fetal body weight) when pregnant rabbits were given oral doses of ≥10 mg/kg rivaroxaban during the period of organogenesis. This dose corresponds to about 4 times the human exposure of unbound drug, based on AUC comparisons at the highest recommended human dose of 20 mg/day. Fetal body weights decreased when pregnant rats were given oral doses of 120 mg/kg. This dose corresponds to about 14 times the human exposure of unbound drug.

8.2 Labor and Delivery

Safety and effectiveness of XARELTO during labor and delivery have not been studied in clinical trials. However, in animal studies maternal bleeding and maternal and fetal death occurred at the rivaroxaban dose of 40 mg/kg (about 6 times maximum human exposure of the unbound drug at the human dose of 20 mg/day).

8.3 Nursing Mothers

It is not known if rivaroxaban is excreted in human milk. Rivaroxaban and/or its metabolites were excreted into the milk of rats. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from rivaroxaban, a decision should be made whether to discontinue nursing or discontinue XARELTO, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of patients in the RECORD 1-3 clinical studies evaluating XARELTO, about 54% were 65 years and over, while about 15% were >75 years. In ROCKET AF, approximately 77% were 65 years and over and about 38% were >75 years. In clinical trials the efficacy of XARELTO in the elderly (65 years or older) was similar to that seen in patients younger than 65 years. Both thrombotic and bleeding event rates were higher in these older patients, but the risk-benefit profile was favorable in all age groups *[see Clinical Pharmacology (12.3) and Clinical Studies (14)]*.

8.6 Females of Reproductive Potential

Females of reproductive potential requiring anticoagulation should discuss pregnancy planning with their physician.

8.7 Renal Impairment

The safety and pharmacokinetics of single-dose XARELTO (10 mg) were evaluated in a study in healthy subjects [CrCl ≥80 mL/min (n=8)] and in subjects with varying degrees of renal impairment (see Table 4). Compared to healthy subjects with normal creatinine clearance, rivaroxaban exposure increased in subjects with renal impairment. Increases in pharmacodynamic effects were also observed.

Table 4: Percent Increase of Rivaroxaban PK and PD Parameters from Normal in Subjects with Renal Insufficiency from a Dedicated Renal Impairment Study

Parameter		Renal Impairment Class [CrCl (mL/min)]		
		Mild [50 to 79] N=8	Moderate [30 to 49] N=8	Severe [15 to 29] N=8
Exposure (% increase relative to normal)	AUC	44	52	64
	C_{max}	28	12	26
FXa Inhibition (% increase relative to normal)	AUC	50	86	100
	E_{max}	9	10	12
PT Prolongation (% increase relative to normal)	AUC	33	116	144
	E_{max}	4	17	20

PT = Prothrombin time; FXa = Coagulation factor Xa; AUC = Area under the concentration or effect curve; C_{max} = maximum concentration; E_{max} = maximum effect; and CrCl = creatinine clearance

Patients with renal impairment taking P-gp and weak to moderate CYP3A4 inhibitors may have significant increases in exposure which may increase bleeding risk *[see Drug Interactions (7.6)]*.

Nonvalvular Atrial Fibrillation

In the ROCKET AF trial, patients with CrCl 30 to 50 mL/min were administered XARELTO 15 mg once daily resulting in serum concentrations of rivaroxaban and clinical outcomes similar to those in patients with better renal function administered XARELTO 20 mg once daily. Patients with CrCl 15 to 30 mL/min were not studied, but administration of XARELTO 15 mg once daily is also expected to result in serum concentrations of rivaroxaban similar to those in patients with normal renal function *[see Dosage and Administration (2.1)]*.

Prophylaxis of Deep Vein Thrombosis

The combined analysis of the RECORD 1-3 clinical efficacy studies did not show an increase in bleeding risk for patients with moderate renal impairment and reported a possible increase in total VTE in this population. Observe closely and promptly evaluate any signs or symptoms of blood loss in patients with moderate renal impairment (CrCl 30 to <50 mL/min). Avoid the use of XARELTO in patients with severe renal impairment (CrCl <30 mL/min) *[see Dosage and Administration (2.3) and Warnings and Precautions (5.2)]*.

8.8 Hepatic Impairment

The safety and pharmacokinetics of single-dose XARELTO (10 mg) were evaluated in a study in healthy subjects (n=16) and subjects with varying degrees of hepatic impairment (see Table 5). No patients with severe hepatic impairment (Child-Pugh C) were studied. Compared to healthy subjects with normal liver function, significant increases in rivaroxaban exposure were observed in subjects with moderate hepatic impairment (Child-Pugh B). Increases in pharmacodynamic effects were also observed.

Table 5: Percent Increase of Rivaroxaban PK and PD Parameters from Normal in Subjects with Hepatic Insufficiency from a Dedicated Hepatic Impairment Study

Parameter		Hepatic Impairment Class (Child-Pugh Class)	
		Mild (Child-Pugh A) N=8	Moderate (Child-Pugh B) N=8
Exposure (% increase relative to normal)	AUC	15	127
	C_{max}	0	27
FXa Inhibition (% increase relative to normal)	AUC	8	159
	E_{max}	0	24
PT Prolongation (% increase relative to normal)	AUC	6	114
	E_{max}	2	41

PT = Prothrombin time; FXa = Coagulation factor Xa; AUC = Area under the concentration or effect curve; C_{max} = maximum concentration; E_{max} = maximum effect

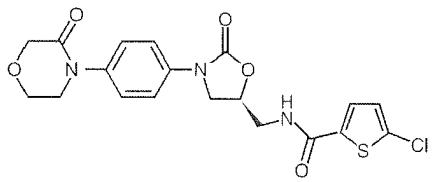
Avoid the use of XARELTO in patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment or with any hepatic disease associated with coagulopathy *[see Dosage and Administration (2.3) and Warnings and Precautions (5.2)]*.

10 OVERDOSAGE

Overdose of XARELTO may lead to hemorrhage. A specific antidote for rivaroxaban is not available. Rivaroxaban systemic exposure is not further increased at single doses >50 mg due to limited absorption. Discontinue XARELTO and initiate appropriate therapy if bleeding complications associated with overdosage occur. The use of activated charcoal to reduce absorption in case of XARELTO overdose may be considered. Due to the high plasma protein binding, rivaroxaban is not expected to be dialyzable *[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)]*.

11 DESCRIPTION

Rivaroxaban, a factor Xa inhibitor, is the active ingredient in XARELTO Tablets with the chemical name 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide. The molecular formula of rivaroxaban is $C_{19}H_{18}ClN_3O_5S$ and the molecular weight is 435.89. The structural formula is:



Rivaroxaban is a pure (*S*)-enantiomer. It is an odorless, non-hygroscopic, white to yellowish powder. Rivaroxaban is only slightly soluble in organic solvents (e.g., acetone, polyethylene glycol 400) and is practically insoluble in water and aqueous media.

Each XARELTO tablet contains 10 mg, 15 mg, or 20 mg of rivaroxaban. The inactive ingredients of XARELTO are: croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate. Additionally, the proprietary film coating mixture used for XARELTO 10 mg tablets is Opadry® Pink and XARELTO 15 mg tablets is Opadry® Red, containing ferric oxide red, hypromellose, polyethylene glycol 3350, and titanium dioxide, and for XARELTO 20 mg tablets is Opadry® II Dark Red, containing ferric oxide red, polyethylene glycol 3350, polyvinyl alcohol (partially hydrolyzed), talc, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

XARELTO is an orally bioavailable factor Xa inhibitor that selectively blocks the active site of factor Xa and does not require a cofactor (such as Anti-thrombin III) for activity. Activation of factor X to factor Xa (FXa) via the intrinsic and extrinsic pathways plays a central role in the cascade of blood coagulation.

12.2 Pharmacodynamics

Dose-dependent inhibition of factor Xa activity was observed in humans and the Neoplastin® prothrombin time (PT), activated partial thromboplastin time (aPTT) and HepTest® are prolonged dose-dependently. Anti-factor Xa activity is also influenced by rivaroxaban.

12.3 Pharmacokinetics

Absorption

The absolute bioavailability of rivaroxaban is dose-dependent. For the 10 mg dose, it is estimated to be 80% to 100% and is not affected by food. XARELTO 10 mg tablets can be taken with or without food *[see Dosage and Administration (2.2)]*.

The absolute bioavailability of rivaroxaban at a dose of 20 mg in the fasted state is approximately 66%. Coadministration of XARELTO with food increases the bioavailability of the 20 mg dose (mean AUC and C_{max} increasing by 39% and 76% respectively with food). XARELTO 15 mg and 20 mg tablets should be taken with the evening meal *[see Dosage and Administration (2.1)]*.

The maximum concentrations (C_{max}) of rivaroxaban appear 2 to 4 hours after tablet intake. The pharmacokinetics of rivaroxaban were not affected by drugs altering gastric pH. Coadministration of XARELTO (30 mg single dose) with the H_2-receptor antagonist ranitidine (150 mg twice daily), the antacid aluminum hydroxide/magnesium hydroxide (10 mL) or XARELTO (20 mg single dose) with the PPI omeprazole (40 mg once daily) did not show an effect on the bioavailability and exposure of rivaroxaban.

Absorption of rivaroxaban is dependent on the site of drug release in the GI tract. A 29% and 56% decrease in AUC and C_{max} compared to tablet was reported when rivaroxaban granulate is released in the proximal small intestine. Exposure is further reduced when drug is released in the distal small intestine, or ascending colon. Avoid administration of rivaroxaban via a method that could deposit drug directly into the proximal small intestine (e.g., feeding tube) which can result in reduced absorption and related drug exposure.

Distribution

Plasma protein binding of rivaroxaban in human plasma is approximately 92% to 95%, with albumin being the main binding component. The steady-state volume of distribution in healthy subjects is approximately 50 L.

Metabolism

Approximately 51% of an orally administered [^{14}C]-rivaroxaban dose was recovered as metabolites in urine (30%) and feces (21%). Oxidative degradation catalyzed by CYP3A4/5 and CYP2J2 and hydrolysis are the major sites of biotransformation. Unchanged rivaroxaban was the predominant moiety in plasma with no major or active circulating metabolites.

Excretion

Following oral administration of a [^{14}C]-rivaroxaban dose, 66% of the radioactive dose was recovered in urine (36% as unchanged drug) and 28% was recovered in feces (7% as unchanged drug). Unchanged drug is excreted into urine, mainly via active tubular secretion and to a lesser extent via glomerular filtration (approximate 5:1 ratio). Rivaroxaban is a substrate of the efflux transporter proteins P-gp and ABCG2 (also abbreviated Bcrp). Rivaroxaban's affinity for influx transporter proteins is unknown.

Rivaroxaban is a low-clearance drug, with a systemic clearance of approximately 10 L/hr in healthy volunteers following intravenous administration. The terminal elimination half-life of rivaroxaban is 5 to 9 hours in healthy subjects aged 20 to 45 years.

Specific Populations

Gender

Gender did not influence the pharmacokinetics or pharmacodynamics of XARELTO.

XARELTO® (rivaroxaban) tablets

Race

Healthy Japanese subjects were found to have 20 to 40% on average, higher exposures compared to other ethnicities including Chinese. However, these differences in exposure are reduced when values are corrected for body weight.

Elderly

In clinical studies, elderly subjects exhibited higher rivaroxaban plasma concentrations than younger subjects with mean AUC values being approximately 50% higher, mainly due to reduced (apparent) total body and renal clearance. Age related changes in renal function may play a role in this age effect. The terminal elimination half-life is 11 to 13 hours in the elderly *[see Use in Specific Populations (8.5)]*.

Body Weight

Extremes in body weight (<50 kg or >120 kg) did not influence (less than 25%) rivaroxaban exposure.

Drug Interactions

In vitro studies indicate that rivaroxaban neither inhibits the major cytochrome P450 enzymes CYP1A2, 2C8, 2C9, 2C19, 2D6, 2J2, and 3A4 nor induces CYP1A2, 2B6, 2C19, or 3A4.

In vitro data also indicates a low rivaroxaban inhibitory potential for P-gp and ABCG2 transporters.

In addition, there were no significant pharmacokinetic interactions observed in studies comparing concomitant rivaroxaban 20 mg and 7.5 mg single dose of midazolam (substrate of CYP3A4), 0.375 mg once-daily dose of digoxin (substrate of P-gp), or 20 mg once daily dose of atorvastatin (substrate of CYP3A4 and P-gp) in healthy volunteers.

12.6 QT/QTc Prolongation

In a thorough QT study in healthy men and women aged 50 years and older, no QTc prolonging effects were observed for XARELTO (15 mg and 45 mg, single-dose).

13 NON-CLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Rivaroxaban was not carcinogenic when administered by oral gavage to mice or rats for up to 2 years. The systemic exposures (AUCs) of unbound rivaroxaban in male and female mice at the highest dose tested (60 mg/kg/day) were 1- and 2-times, respectively, the human exposure of unbound drug at the human dose of 20 mg/day. Systemic exposures of unbound drug in male and female rats at the highest dose tested (60 mg/kg/day) were 2- and 4-times, respectively, the human exposure.

Rivaroxaban was not mutagenic in bacteria (Ames-Test) or clastogenic in V79 Chinese hamster lung cells *in vitro* or in the mouse micronucleus test *in vivo*.

No impairment of fertility was observed in male or female rats when given up to 200 mg/kg/day of rivaroxaban orally. This dose resulted in exposure levels, based on the unbound AUC, at least 13 times the exposure in humans given 20 mg rivaroxaban daily.

14 CLINICAL STUDIES

14.1 Stroke Prevention in Nonvalvular Atrial Fibrillation

The evidence for the efficacy and safety of XARELTO was derived from ROCKET AF, a multi-national, double-blind study comparing XARELTO (at a dose of 20 mg once daily with the evening meal in patients with CrCl >50 mL/min and 15 mg once daily with the evening meal in patients with CrCl 30 to <50 mL/min) to warfarin (titrated to INR 2.0 to 3.0) to reduce the risk of stroke and non-central nervous system (CNS) systemic embolism in patients with nonvalvular atrial fibrillation (AF). Patients had to have one or more of the following additional risk factors for stroke:

- a prior stroke (ischemic or unknown type), transient ischemic attack (TIA) or non-CNS systemic embolism, or
- 2 or more of the following risk factors:
  - o age ≥75 years,
  - o hypertension,
  - o heart failure or left ventricular ejection fraction ≤35%, or
  - o diabetes mellitus

ROCKET AF was a non-inferiority study designed to demonstrate that XARELTO preserved more than 50% of warfarin's effect on stroke and non-CNS systemic embolism as established by previous placebo-controlled studies of warfarin in atrial fibrillation.

A total of 14264 patients were randomized and followed on study treatment for a median of 590 days. The mean age was 71 years and the mean $CHADS_2$ score was 3.5. The population was 60% male, 83% Caucasian, 13% Asian and 1.3% Black. There was a history of stroke, TIA, or non-CNS systemic embolism in 55% of patients, and 38% of patients had not taken a vitamin K antagonist (VKA)

within 6 weeks at time of screening. Concomitant diseases of patients in this study included hypertension 91%, diabetes 40%, congestive heart failure 63%, and prior myocardial infarction 17%. At baseline, 37% of patients were on aspirin (almost exclusively at a dose of 100 mg or less) and few patients were on clopidogrel. Patients were enrolled in Eastern Europe (39%); North America (19%); Asia, Australia, and New Zealand (15%); Western Europe (15%); and Latin America (13%). Patients randomized to warfarin had a mean percentage of time in the INR target range of 2.0 to 3.0 of 55%, lower during the first few months of the study.

In ROCKET AF, XARELTO was demonstrated non-inferior to warfarin for the primary composite endpoint of time to first occurrence of stroke (any type) or non-CNS systemic embolism [HR (95% CI): 0.88 (0.74, 1.03)], but superiority to warfarin was not demonstrated. There is insufficient experience to determine how XARELTO and warfarin compare when warfarin therapy is well-controlled.

Table 6 displays the overall results for the primary composite endpoint and its components.

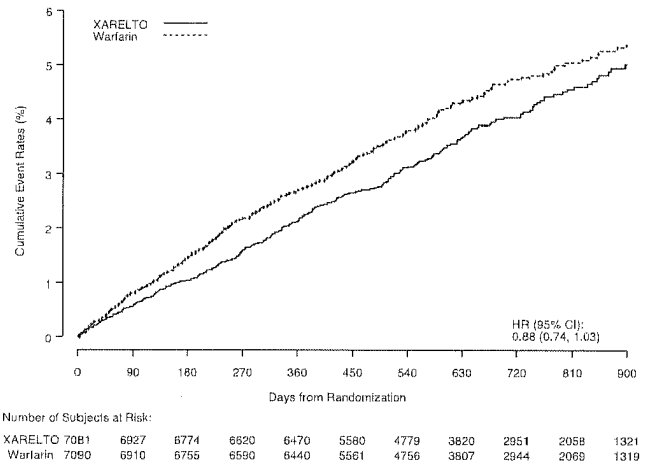
Table 6: Primary Composite Endpoint Results in ROCKET AF Study

	XARELTO		Warfarin		XARELTO vs. Warfarin
Event	**N = 7081 n (%)**	**Event Rate (per 100 Pt-yrs)**	**N = 7090 n (%)**	**Event Rate (per 100 Pt-yrs)**	**Hazard Ratio (95% CI)**
Primary Composite Endpoint*	269 (3.8)	2.1	306 (4.3)	2.4	0.88 (0.74, 1.03)
Stroke	253 (3.6)	2.0	281 (4.0)	2.2	
Hemorrhagic Stroke	33 (0.5)	0.3	57 (0.8)	0.4	
Ischemic Stroke	206 (2.9)	1.6	208 (2.9)	1.6	
Unknown Stroke Type	19 (0.3)	0.2	18 (0.3)	0.1	
Non-CNS Systemic Embolism	20 (0.3)	0.2	27 (0.4)	0.2	

*The primary endpoint was the time to first occurrence of stroke (any type) or non-CNS systemic embolism. Data are shown for all randomized patients followed to site notification that the study would end.

Figure 1 is a plot of the time from randomization to the occurrence of the first primary endpoint event in the two treatment arms.

Figure 1: Time to First Occurrence of Stroke (any type) or Non-CNS Systemic Embolism by Treatment Group



The efficacy of XARELTO was generally consistent across major subgroups.

The protocol for ROCKET AF did not stipulate anticoagulation after study drug discontinuation, but warfarin patients who completed the study were generally maintained on warfarin. XARELTO patients were generally switched to warfarin without a period of co-administration of warfarin and XARELTO, so that they were not adequately anticoagulated after stopping XARELTO until attaining a therapeutic INR. During the 28 days following the end of the study, there were 22 strokes in the 4637 patients taking XARELTO vs. 6 in the 4691 patients taking warfarin.

XARELTO® (rivaroxaban) tablets

Few patients in ROCKET AF underwent electrical cardioversion for atrial fibrillation. The utility of XARELTO for preventing post-cardioversion stroke and systemic embolism is unknown.

14.2 Prophylaxis of Deep Vein Thrombosis

XARELTO was studied in 9011 patients (4487 XARELTO-treated, 4524 enoxaparin-treated patients) in the RECORD 1, 2, and 3 studies.

The two randomized, double-blind, clinical studies (RECORD 1 and 2) in patients undergoing elective total hip replacement surgery compared XARELTO 10 mg once daily starting at least 6 to 8 hours (about 90% of patients dosed 6 to 10 hours) after wound closure versus enoxaparin 40 mg once daily started 12 hours preoperatively. In RECORD 1 and 2, a total of 6727 patients were randomized and 6579 received study drug. The mean age [± standard deviation (SD)] was 63 ± 12.2 (range 18 to 93) years with 49% of patients ≥65 years and 55% of patients were female. More than 82% of patients were White, 7% were Asian, and less than 2% were Black. The studies excluded patients undergoing staged bilateral total hip replacement, patients with severe renal impairment defined as an estimated creatinine clearance <30 mL/min, or patients with significant liver disease (hepatitis or cirrhosis). In RECORD 1, the mean exposure duration (± SD) to active XARELTO and enoxaparin was 33.3 ± 7.0 and 33.6 ± 8.3 days, respectively. In RECORD 2, the mean exposure duration to active XARELTO and enoxaparin was 33.5 ± 6.9 and 12.4 ± 2.9 days, respectively. After Day 13, oral placebo was continued in the enoxaparin group for the remainder of the double-blind study duration. The efficacy data for RECORD 1 and 2 are provided in Table 7.

Table 7: Summary of Key Efficacy Analysis Results for Patients Undergoing Total Hip Replacement Surgery - Modified Intent-to-Treat Population

	RECORD 1			RECORD 2		
Treatment Dosage and Duration	**XARELTO 10 mg once daily**	**Enoxaparin 40 mg once daily**	**RRR*, p-value**	**XARELTO 10 mg once daily**	**Enoxaparin† 40 mg once daily**	**RRR*, p-value**
Number of Patients	**N = 1513**	**N = 1473**		**N = 834**	**N = 835**	
Total VTE	17 (1.1%)	57 (3.9%)	71% (95% CI: 50, 83), p<0.001	17 (2.0%)	70 (8.4%)	76% (95% CI: 59, 86), p<0.001
Components of Total VTE						
Proximal DVT	1 (0.1%)	31 (2.1%)		5 (0.6%)	40 (4.8%)	
Distal DVT	12 (0.8%)	26 (1.8%)		11 (1.3%)	43 (5.2%)	
Non-fatal PE	3 (0.2%)	1 (0.1%)		1 (0.1%)	4 (0.5%)	
Death (any cause)	4 (0.3%)	4 (0.3%)		2 (0.2%)	4 (0.5%)	
Number of Patients	**N= 1600**	**N = 1587**		**N= 928**	**N = 929**	
Major VTE‡	3 (0.2%)	33 (2.1%)	91% (95% CI: 71, 97), p<0.001	6 (0.7%)	45 (4.8%)	87% (95% CI: 69, 94), p<0.001
Number of Patients	**N = 2103**	**N = 2119**		**N = 1178**	**N = 1179**	
Symptomatic VTE	5 (0.2%)	11 (0.5%)		3 (0.3%)	15 (1.3%)	

* Relative Risk Reduction; CI=confidence interval
† Includes the placebo-controlled period of RECORD 2
‡ Proximal DVT, nonfatal PE or VTE-related death

One randomized, double-blind, clinical study (RECORD 3) in patients undergoing elective total knee replacement surgery compared XARELTO 10 mg once daily started at least 6 to 8 hours (about 90% of patients dosed 6 to 10 hours) after wound closure versus enoxaparin. In RECORD 3, the enoxaparin regimen was 40 mg once daily started 12 hours preoperatively. The mean age (± SD) of patients in the study was 68 ± 9.0 (range 28 to 91) years with 66% of patients ≥65 years. Sixty-eight percent (68%) of patients were female. Eighty-one percent (81%) of patients were White, less than 7% were Asian, and less than 2% were Black. The study excluded patients with severe renal impairment defined as an estimated creatinine clearance <30 mL/min or patients with significant liver disease (hepatitis or cirrhosis). The mean exposure duration (± SD) to active XARELTO and enoxaparin was 11.9 ± 2.3 and 12.5 ± 3.0 days, respectively. The efficacy data are provided in Table 8.

Table 8: Summary of Key Efficacy Analysis Results for Patients Undergoing Total Knee Replacement Surgery - Modified Intent-to-Treat Population

	RECORD 3		
Treatment Dosage and Duration	**XARELTO 10 mg once daily**	**Enoxaparin 40 mg once daily**	**RRR*, p-value**
Number of Patients	**N = 813**	**N = 871**	
Total VTE	79 (9.7%)	164 (18.8%)	48% (95% CI: 34, 60), p<0.001
Components of events contributing to Total VTE			
Proximal DVT	9 (1.1%)	19 (2.2%)	
Distal DVT	74 (9.1%)	154 (17.7%)	
Non-fatal PE	0	4 (0.5%)	
Death (any cause)	0	2 (0.2%)	
Number of Patients	**N = 895**	**N = 917**	
Major VTE†	9 (1.0%)	23 (2.5%)	60% (95% CI: 14, 81), p=0.024
Number of Patients	**N = 1206**	**N = 1226**	
Symptomatic VTE	8 (0.7%)	24 (2.0%)	

* Relative Risk Reduction; CI=confidence interval

† Proximal DVT, nonfatal PE or VTE-related death

16 HOW SUPPLIED/STORAGE AND HANDLING

XARELTO (rivaroxaban) Tablets are available in the strengths and packages listed below:

- 10 mg tablets are round, light red, biconvex film-coated tablets marked with a triangle pointing down above a "10" on one side, and an "Xa" on the other side. The tablets are supplied in the packages listed:

  NDC 50458-580-30 Bottle containing 30 tablets

  NDC 50458-580-10 Blister package containing 100 tablets (10 blister cards containing 10 tablets each)

- 15 mg tablets are round, red, biconvex film-coated tablets with a triangle pointing down above a "15" marked on one side and "Xa" on the other side. The tablets are supplied in the packages listed:

  NDC 50458-578-30 Bottle containing 30 tablets

  NDC 50458-578-90 Bottle containing 90 tablets

  NDC 50458-578-10 Blister package containing 100 tablets (10 blister cards containing 10 tablets each)

- 20 mg tablets are triangle-shaped, dark red film-coated tablets with a triangle pointing down above a "20" marked on one side and "Xa" on the other side. The tablets are supplied in the packages listed:

  NDC 50458-579-30 Bottle containing 30 tablets

  NDC 50458-579-90 Bottle containing 90 tablets

  NDC 50458-579-10 Blister package containing 100 tablets (10 blister cards containing 10 tablets each)

Store at 25° C (77° F) or room temperature; excursions permitted to 15°-30° C (59°-86° F) [see USP Controlled Room Temperature].

Keep out of the reach of children.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

17.1 Instructions for Patient Use

- Advise patients to take XARELTO only as directed.
- Remind patients to not discontinue XARELTO without first talking to their healthcare professional.
- Advise patients with atrial fibrillation to take XARELTO once daily with the evening meal.
- If a dose is missed, advise the patient to take XARELTO as soon as possible on the same day and continue on the following day with their recommended daily dose regimen.

XARELTO® (rivaroxaban) tablets

17.2 Bleeding Risks

- Advise patients to report any unusual bleeding or bruising to their physician. Inform patients that it might take them longer than usual to stop bleeding, and that they may bruise and/or bleed more easily when they are treated with XARELTO *[see Warnings and Precautions (5.2)]*.
- If patients have had neuraxial anesthesia or spinal puncture, and particularly, if they are taking concomitant NSAIDs or platelet inhibitors, advise patients to watch for signs and symptoms of spinal or epidural hematoma, such as tingling, numbness (especially in the lower limbs) and muscular weakness. If any of these symptoms occur, advise the patient to contact his or her physician immediately *[see Boxed Warning]*.

17.3 Invasive or Surgical Procedures

Instruct patients to inform their health care professional that they are taking XARELTO before any invasive procedure (including dental procedures) is scheduled.

17.4 Concomitant Medication and Herbals

Advise patients to inform their physicians and dentists if they are taking, or plan to take, any prescription or over-the-counter drugs or herbals, so their healthcare professionals can evaluate potential interactions *[see Drug Interactions (7)]*.

17.5 Pregnancy and Pregnancy-Related Hemorrhage

- Advise patients to inform their physician immediately if they become pregnant or intend to become pregnant during treatment with XARELTO *[see Use in Specific Populations (8.1)]*.
- Advise pregnant women receiving XARELTO to immediately report to their physician any bleeding or symptoms of blood loss *[see Warnings and Precautions (5.4)]*.

17.6 Nursing

Advise patients to discuss with their physician if they are nursing or intend to nurse during anticoagulant treatment *[see Use in Specific Populations (8.3)]*.

17.7 Females of Reproductive Potential

Advise patients who can become pregnant to discuss pregnancy planning with their physician *[see Use in Specific Populations (8.6)]*.

Active Ingredient Made in Germany

Finished Product Manufactured by:
Janssen Ortho, LLC
Gurabo, PR 00778

Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560

Licensed from:
Bayer HealthCare AG
51368 Leverkusen, Germany

10185201

MEDICATION GUIDE

XARELTO® (zah-REL-toe)
(rivaroxaban)

Tablets

Read this Medication Guide before you start taking XARELTO and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your doctor about your medical condition or your treatment.

What is the most important information I should know about XARELTO?

- **For people taking XARELTO for atrial fibrillation:**

  People with atrial fibrillation (an irregular heart beat) are at an increased risk of forming a blood clot in the heart, which can travel to the brain, causing a stroke, or to other parts of the body. XARELTO lowers your chance of having a stroke by helping to prevent clots from forming. If you stop taking XARELTO, you may have increased risk of forming a clot in your blood.

  Do not stop taking XARELTO without talking to the doctor who prescribes it for you. Stopping XARELTO increases your risk of having a stroke.

  If you have to stop taking XARELTO, your doctor may prescribe another blood thinner medicine to prevent a blood clot from forming.

- XARELTO can cause bleeding which can be serious, and rarely may lead to death. This is because XARELTO is a blood thinner medicine that reduces blood clotting. While you take XARELTO you are likely to bruise more easily and it may take longer for bleeding to stop.

  You may have a higher risk of bleeding if you take XARELTO and take other medicines that increase your risk of bleeding, including:

  - aspirin or aspirin containing products
  - non-steroidal anti-inflammatory drugs (NSAIDs)
  - warfarin sodium (Coumadin®, Jantoven®)
  - any medicine that contains heparin
  - clopidogrel (Plavix®)
  - prasugrel (Effient®)
  - ticagrelor (Brilinta®)

  Tell your doctor if you take any of these medicines. Ask your doctor or pharmacist if you are not sure if your medicine is one listed above.

  Call your doctor or get medical help right away if you develop any of these signs or symptoms of bleeding:

  - unexpected bleeding or bleeding that lasts a long time, such as:
    - nose bleeds that happen often
    - unusual bleeding from the gums
    - menstrual bleeding that is heavier than normal or vaginal bleeding
  - bleeding that is severe or you cannot control
  - red, pink or brown urine
  - bright red or black stools (looks like tar)
  - cough up blood or blood clots
  - vomit blood or your vomit looks like "coffee grounds"
  - headaches, feeling dizzy or weak
  - pain, swelling, or new drainage at wound sites

XARELTO® (rivaroxaban) tablets

See "What are the possible side effects of XARELTO?" for more information about side effects.

What is XARELTO?

- XARELTO is a prescription medicine used to:
  - reduce the risk of stroke and blood clots in people who have a medical condition called atrial fibrillation. With atrial fibrillation, part of the heart does not beat the way it should. This can lead to the formation of blood clots, which can travel to the brain, causing a stroke, or to other parts of the body.
  - reduce the risk of forming a blood clot in the legs and lungs of people who have just had hip or knee replacement surgery.

It is not known if XARELTO is safe and works in children.

Who should not take XARELTO?
Do not take XARELTO if you:

- currently have certain types of abnormal bleeding. Talk to your doctor before taking XARELTO if you currently have unusual bleeding.
- are allergic to rivaroxaban or any of the ingredients in XARELTO. See the end of this leaflet for a complete list of ingredients in XARELTO.

What should I tell my doctor before taking XARELTO?
Before you take XARELTO, tell your doctor if you:

- have ever had bleeding problems
- have liver or kidneys problems
- have any other medical condition
- are pregnant or planning to become pregnant. It is not known if XARELTO will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if XARELTO passes into your breast milk. You and your doctor should decide if you will take XARELTO or breastfeed.

Tell all of your doctors and dentists that you are taking XARELTO. They should talk to the doctor who prescribed XARELTO for you before you have any surgery, medical or dental procedure.

Tell your doctor about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements. Some of your other medicines may affect the way XARELTO works. Certain medicines may increase your risk of bleeding. See **"What is the most important information I should know about XARELTO?"**

Especially tell your doctor if you take:

- ketoconazole (Nizoral®)
- itraconazole (Onmel™, Sporanox®)
- ritonavir (Norvir®)
- lopinavir/ritonavir (Kaletra®)
- indinavir (Crixivan®)
- carbamazepine (Carbatrol®, Equetro®, Tegretol®, Tegretol®-XR, Teril™, Epitol®)
- phenytoin (Dilantin-125®, Dilantin®, Phenobarbital, Solfoton™)
- rifampin (Rifater®, Rifamate®, Rimactane®, Rifadin®)
- St. John's wort (Hypericum perforatum)

Ask your doctor if you are not sure if your medicine is one listed above.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I take XARELTO?

- Take XARELTO exactly as prescribed by your doctor. Do not change your dose or stop taking XARELTO unless your doctor tells you to.
- For people who have:
  - o **atrial fibrillation:** Take XARELTO 1 time a day **with your evening meal. Stopping XARELTO may increase your risk of having a stroke or forming blood clots in other parts of your body.**
  - o **hip or knee replacement surgery:** Take XARELTO 1 time a day **with or without food.**
- **Your doctor will decide how long you should take XARELTO. Do not stop taking XARELTO without talking with your doctor first.**
- Your doctor may stop XARELTO for a short time before any surgery, medical or dental procedure. Your doctor will tell you when to start taking XARELTO again after your surgery or procedure.
- Do not run out of XARELTO. Refill your prescription of XARELTO before you run out. When leaving the hospital following a hip or knee replacement, be sure that you will have XARELTO available to avoid missing any doses.
- If you miss a dose of XARELTO, take it as soon as you remember on the same day.
- If you take too much XARELTO, go to the nearest hospital emergency room or call your doctor right away.

What are the possible side effects of XARELTO?

- **See "What is the most important information I should know about XARELTO?"**

Tell your doctor if you have any side effect that bothers you or that does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store XARELTO?

- Store XARELTO at room temperature between 59° to 86°F (15° to 30° C).

Keep XARELTO and all medicines out of the reach of children.

General information about XARELTO.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use XARELTO for a condition for which it was not prescribed. Do not give XARELTO to other people, even if they have the same condition. It may harm them.

This Medication Guide summarizes the most important information about XARELTO. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about XARELTO that is written for health professionals.

For more information call 1-800-526-7736 or go to www.XARELTO-US.com.

What are the ingredients in XARELTO?

Active ingredient: rivaroxaban

Inactive ingredients: croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate.

XARELTO® (rivaroxaban) tablets

The proprietary film coating mixture for XARELTO 10 mg tablets is Opadry® Pink contains: ferric oxide red, hypromellose, polyethylene glycol 3350, and titanium dioxide.

The proprietary film coating mixture for XARELTO 15 mg tablets is Opadry® Red, contains: ferric oxide red, hypromellose, polyethylene glycol 3350, and titanium dioxide.

The proprietary film coating mixture for XARELTO 20 mg tablets is Opadry® II Dark Red, contains: ferric oxide red, polyethylene glycol 3350, polyvinyl alcohol (partially hydrolyzed), talc, and titanium dioxide.

Issued: November 2011

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Finished Product Manufactured by:
Janssen Ortho, LLC
Gurabo, PR 00778

Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560

Licensed from:
Bayer HealthCare AG
51368 Leverkusen, Germany

janssen

10185201

02X11309A

Electronic Acknowledgement Receipt

EFS ID:	11951697
Application Number:	11883218
International Application Number:	
Confirmation Number:	9960
Title of Invention:	Prevention and Treatment of Thromboembolic Disorders
First Named Inventor/Applicant Name:	Frank Misselwitz
Customer Number:	23416
Filer:	Christine Hansen/Sara Maloney
Filer Authorized By:	Christine Hansen
Attorney Docket Number:	11987-00042
Receipt Date:	30-JAN-2012
Filing Date:	16-JUL-2008
Time Stamp:	15:01:47
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		Response_Final_OA.pdf	1698237 7099515ebf9fd6b8bc83e2230a12da08e1b9eb96	yes	21

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment After Final	1	1
	Claims	2	3
	Applicant Arguments/Remarks Made in an Amendment	4	21
Warnings:			
Information:			
	Total Files Size (in bytes):	1698237	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 11/883,218	Filing Date 07/16/2008	☐ To be Mailed

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☐		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	01/30/2012	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 12	Minus	** 20	= 0	X $ =		OR	X $60=	0
	Independent (37 CFR 1.16(h))	* 2	Minus	***3	= 0	X $ =		OR	X $250=	0
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/VICTOR BARLOW/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/883,218	07/16/2008	Frank Misselwitz	11987-00042	9960

23416 7590 09/21/2011

CONNOLLY BOVE LODGE & HUTZ, LLP
P O BOX 2207
WILMINGTON, DE 19899

EXAMINER	
KAROL, JODY LYNN	

ART UNIT	PAPER NUMBER
1627	

MAIL DATE	DELIVERY MODE
09/21/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	11/883,218	MISSELWITZ ET AL.	
	Examiner	Art Unit	
	JODY KAROL	1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 June 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1,4,5,7-9,11 and 15-19* is/are pending in the application.

5a) Of the above claim(s) *7-9,15-17 and 19* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1,4,5,11 and 18* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/17/2011*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of applicant's Amendment/Remarks filed 6/17/2011. Claims 1, 5, 9, and 11 have been amended. Claims 2, 3, 6, 10, and 12-14 are cancelled. Claims 15-19 are newly added. Claims 7-8 remain withdrawn as pertaining to the non-elected invention. Claim 9 has been amended to as to pertain to the non-elected invention. New claims 12-17 and 19 are withdrawn as pertaining to the non-elected invention. Claims 1, 4, 5, 7-9, 11, and 15-19 are pending. Claims 1, 4, 5, 11, and 18 are currently under consideration.

Information Disclosure Statement

1. The information disclosure statement (IDS) filed on 6/17/2011 is in compliance with the provisions of 37 CFR 1.97. However, the NPL references have not been considered because English language translations of the documents were not provided, and their relevance to the application has not been indicated.

WITHDRAWN REJECTIONS

2. In view of Applicant's cancellation of claims 2, 6, 10, and 12-14 and amendment of claim 9 to a non-elected invention, the rejection of claims 2, 6, 9, 10, and 12-14 on the ground on nonstatutory obviousness-type double patenting as being unpatentable over claims 12, 24, and 30 of U.S. Patent No. 7,157,456

B2 in view of Kubitza et al.[1] ("Multiple dose escalation study investigating the pharmacodynamics, safety, and pharmacokinetics of BAY 59-7939 an oral, direct Factor Xa inhibitor in healthy male subjects," *Blood*, Vol. 102:11 16 Nov. 2003, pgs 811a - cited on IDS) and Kubitza et al.[2] (ABSTRACT 2010, "Single Dose escalation study investigating the pharmacodynamics, safety, and pharmacokinetics of BAY 59-7939 an oral, direct Factor Xa inhibitor in healthy male subjects," *Blood*, Vol. 102:11, 16 Nov. 2003, page 813a - cited on IDS).

3. In view of Applicant's cancellation of claims 2, 6, 10, and 12-14 and amendment of claim 9 to a non-elected invention, the rejection of claims 2, 6, 9, 10, and 12-14 on the ground on nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6 and 17-21 of U.S. Patent No. 7,592,339 B2 in view of Kubitza et al.[1] ("Multiple dose escalation study investigating the pharmacodynamics, safety, and pharmacokinetics of BAY 59-7939 an oral, direct Factor Xa inhibitor in healthy male subjects," *Blood*, Vol. 102:11 16 Nov. 2003, pgs 811a - cited on IDS) and Kubitza et al.[2] (ABSTRACT 2010, "Single Dose escalation study investigating the pharmacodynamics, safety, and pharmacokinetics of BAY 59-7939 an oral, direct Factor Xa inhibitor in healthy male subjects," *Blood*, Vol. 102:11, 16 Nov. 2003, page 813a - cited on IDS).

4. In view of Applicant's amendments to claims 1 and 9 and cancellation of claims 2 and 10, the rejection of claims 1, 2, 4, 5, and 9-11 under 35 U.S.C. 112, 1st paragraph, for lack of full enablement is herein withdrawn.

5. In view of Applicant's cancellation of claims 2, 6, 10, and 12-14 and amendment of claim 9, the rejection of claims 2, 6, 9, 10, and 12-14 under 35 U.S.C. 103(a) as being unpatentable over Straub et al. (US 2003/056310 A1) in view of Kubitza et al.[1] ("Multiple dose escalation study investigating the pharmacodynamics, safety, and pharmacokinetics of BAY 59-7939 an oral, direct Factor Xa inhibitor in healthy male subjects," *Blood*, Vol. 102:11 16 Nov. 2003, pgs 811a - cited on IDS) and Kubitza et al.[2] (ABSTRACT 2010, "Single Dose escalation study investigating the pharmacodynamics, safety, and pharmacokinetics of BAY 59-7939 an oral, direct Factor Xa inhibitor in healthy male subjects," *Blood*, Vol. 102:11, 16 Nov. 2003, page 813a - cited on IDS) is herein withdrawn.

Response to Arguments

6. Applicant's arguments filed 6/17/2011 have been fully considered but they are not persuasive.

Applicant argues that the patented claims and Straub et al. do not disclose the presently claimed once daily dosage for at least five consecutive days of a rapid -release oral dosage form and that Kubitza et al.[1] and Kubitza et al.[2] do not provide the missing teaching because they report the pharmacokinetic studies of rivaroxaban in healthy subjects. Applicants further argue that neither reference discloses the dosages required for efficacy in patients suffering from, or at risk from, a thromboembolic disorder or that an efficacious dose would be a rapid-

release oral dosage form administered once daily. In response it is respectfully submitted that the term “treatment" in the instant claims is defined to include prophylactic treatment of thromboembolic disorders. Thus, the patient population is interpreted to include healthy subjects since anyone could potentially be at risk for deep venous thrombosis. Further, Kubitza et al.[1] teach administration of rivaroxaban orally once daily for five days Kubitza et al.[2]teach rivaroxaban has a rapid onset of action, indicating the tablets are rapidly releasing the active compound. It is also noted that the instantly recited claims do not specify a dosage amount.

Applicants argue that one of ordinary skill in the art looking for an effective dose of rivaroxaban would have looked at half-life and pharmacokinetics of rivaroxaban leading away from once daily dosing with a rapid-release oral dosage form. Applicants argue that it was well known to a person of ordinary skill in the art that a drug having a half-life of ten hours or less usually cannot be efficacious with once daily oral administration of a rapid-release form. In response it is respectfully submitted that Kubitza et al.[1] and Kubitza et al.[2] both teach once daily dosing of a rapidly releasing tablet. Further, a once daily dosage at a higher dosage is sometimes preferred in instances where patient compliance is an issue.

Applicant alleges that “[i]t had been demonstrated by preclinical investigations that the k_i value for free factor Xa is 0.4 nM, which would be equivalent to a plasma concentration of approximately 0.17 mg/L of unbound rivaroxaban. The administration of 10 mg rivaroxaban once daily in phase II

studies resulted in free plasma concentrations at rough of 0.91 mg/L, which is approximately five-fold higher than the k_i value for free factor Xa. Therefore, the offset of action can be described by the elimination of rivaroxaban from the plasma, which based on an elimination half-life of 11-13 hours, can be assumed to be between 48-72 hours after the last intake of rivaroxaban 10 mg rapid release tablet." It appears that Applicant is alleging unexpected results. In response it is respectfully submitted that it is applicant's burden to demonstrate unexpected results over the prior art. See MPEP 716.02, also 716.02 (a) - (g). Furthermore, the unexpected results should be demonstrated with evidence that the differences in results are in fact unexpected and unobvious and of both statistical and practical significance. *Ex parte Gelles*, 22 USPQ2d 1318, 1319 (Bd. Pat. App. & Inter. 1992). Moreover, evidence as to any unexpected benefits must be "clear and convincing" *In re Lohr*, 137 USPQ 548 (CCPA 1963), and be of a scope reasonably commensurate with the scope of the subject matter claimed, *In re Linder*, 173 USPQ 356 (CCPA 1972).

In the instant case, the evidence presented is not clear. The preclinical data Applicant refers to has not been provided in the instant specification (or a declaration) and it is not clear how Applicant has arrived at the data referred to in the remarks. The statements concerning the plasma half-life of rivaroxaban (4-6 hours on page 4 of the remarks) and the elimination half-life of rivaroxaban (11-13 hours on page 6 of the remarks) appear to be contradictory. In regards to the data referred to on page 7 of the remarks concerning Table 1-1 (page 13 of the instant specification), 30 mg od rivaroxaban is in line with results from 30 mg bid

rivaroxaban. However, it is noted that the total dosage for the od versus the bid rivaroxaban is not the same (30 mg versus 60 mg). Furthermore, the 20 mg bid rivaroxaban seems to be the most effective (i.e. a dosage of 40 mg). The data referred to in Table 1-2 (page 14 of the instant specification) seems to indicate higher dosages were associated with increased bleeding events (i.e. 0% for 2.5 mg bid versus 4.5% for 30 mg od or 10.8% for 30 mg bid). Therefore, no clear and convincing unexpected benefit is seen to be present herein. Thus, the instant claims are still considered properly rejected under 35 USC 103(a).

Thus, for these reasons, Applicant's arguments are found unpersuasive. Said rejection is maintained.

MAINTAINED REJECTIONS

7. The following rejections have been maintained from the previous Office Action dated 3/17/2011 but have been slightly modified to account Applicant's amendments to claims 1, 5, and 11 and for new claim 18:

Double Patenting

8. Claims 1, 4, 5, 11, and 18 are directed to an invention not patentably distinct from claims 13, 24, and 30 of commonly assigned US 7,157,456 B2. Specifically, the instant claims and the patented claims are both directed to methods of treating thromboembolic disorders comprising administering 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-mopholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide (rivaroxaban).

9. Claims 1, 4, 5, 11, and 18 are directed to an invention not patentably distinct from claims 1-6 and 17-21 of commonly assigned US 7,592,399 B2. Specifically, the instant claims and the patented claims are both directed to methods of treating thromboembolic disorders comprising administering 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-mopholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide (rivaroxaban).

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned US 7,157,456 B2, US 7,592,399 B2, and US Application No. 11/317,720 discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

Nonstatutory Double Patenting

10. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 1, 4, 5, 11, and 18 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 13, 24, and 30 of U.S. Patent No. 7,157,456 B2 in view of Kubitza et al.[1] ("Multiple dose escalation study investigating the pharmacodynamics, safety, and pharmacokinetics of BAY 59-7939 an oral, direct Factor Xa inhibitor in healthy male subjects," *Blood*, Vol. 102:11 16 Nov. 2003, pgs 811a - cited on IDS) and Kubitza et al.[2] (ABSTRACT 2010, "Single Dose escalation study investigating the pharmacodynamics, safety, and pharmacokinetics of BAY 59-7939 an oral, direct

Factor Xa inhibitor in healthy male subjects," *Blood*, Vol. 102:11, 16 Nov. 2003, page 813a - cited on IDS).

Although the conflicting claims are not identical, they are not patentably distinct from each other because they are both directed to methods of treating thromboembolic disorders comprising administering 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-mopholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide (rivaroxaban).

The patented claims do not teach administering 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-mopholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide (rivaroxaban) once daily for at least five consecutive days. The patented claims do not teach the plasma concentration half-life in a human patient or that the dosage form is a rapid release.

Kubitza et al.[1] teach administering 5 mg of BAY 59-7939 (rivaroxaban) once daily to male subjects on day 0 and days 4-8 (i.e. five consecutive days) (see page 811a, subjects and methods).

Kubitza et al.[2] teach administering 1.25 mg to 80 mg of BAY 59-7939 (rivaroxaban) under fasting conditions as a tablet to men, wherein BAY 59-7939 showed rapid onset of action (i.e. rapid release). Kubitza et al. also teach the plasma concentration half-life of the tablet containing BAY 59-7939 was observed 2 hours after administration. Kubitza et al. further teach BAY 59-7939 is safe and well-tolerated across a wide range of oral doses (1.25 mg to 80 mg) (see abstract# 3010).

It would have been obvious to one of ordinary skill in the art at the time of the invention to treat deep venous thromboses in a patient by administering rivaroxaban as disclosed by the patented claims using the administration guidelines and tablets taught by Kubitza et al.[1] and Kubitza et al.[2] One of ordinary skill in the art would have been motivated to administer rivaroxaban for 5 consecutive days as taught by Kubitza et al.[1] in order to effectively treat deep vein thromboses. One of ordinary skill in the art would have been motivated to administer rivaroxaban once daily using the rapid release tablet Kubitza et al.[2] in order to provide patient convenience and compliance. One of ordinary skill in the art would have had a reasonable expectation of success in treating deep venous thromboses in a patient by administering rivaroxaban as disclosed by the patented claims using the administration guidelines and tablets taught by Kubitza et al.[1] and Kubitza et al.[2] because rivaroxaban is known to treat deep venous thromboses, and Kubitza et al.[1] and Kubitza et al.[2] teach administration guidelines for rivaroxaban that are safe and tolerable for patients.

12. Claims 1, 4, 5, 11, and 18 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6 and 17-21 of U.S. Patent No. 7,592,339 B2 in view of Kubitza et al.[1] ("Multiple dose escalation study investigating the pharmacodynamics, safety, and pharmacokinetics of BAY 59-7939 an oral, direct Factor Xa inhibitor in healthy male subjects," *Blood*, Vol. 102:11 16 Nov. 2003, pgs 811a - cited on IDS) and Kubitza et al.[2] (ABSTRACT 2010, "Single Dose escalation study investigating the

pharmacodynamics, safety, and pharmacokinetics of BAY 59-7939 an oral, direct Factor Xa inhibitor in healthy male subjects," *Blood*, Vol. 102:11, 16 Nov. 2003, page 813a - cited on IDS).

Although the conflicting claims are not identical, they are not patentably distinct from each other because they are both directed to methods of treating thromboembolic disorders comprising administering 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-mopholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide (rivaroxaban)..

The patented claims do not teach administering 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-mopholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide (rivaroxaban) once daily for at least five consecutive days. The patented claims do not teach the plasma concentration half-life in a human patient. The patented claims do not teach a rapid release tablet as claimed in the instant claims 5, 10, 11, and 14.

Kubitza et al.[1] teach administering 5 mg of BAY 59-7939 (rivaroxaban) once daily to male subjects on day 0 and days 4-8 (i.e. five consecutive days) (see page 811a, subjects and methods).

Kubitza et al.[2] teach administering 1.25 mg to 80 mg of BAY 59-7939 (rivaroxaban) under fasting conditions as a tablet to men, wherein BAY 59-7939 showed rapid onset of action (i.e. rapid release). Kubitza et al. also teach the plasma concentration half-life of the tablet containing BAY 59-7939 was observed 2 hours after administration. Kubitza et al. further teach BAY 59-7939

is safe and well-tolerated across a wide range of oral doses (1.25 mg to 80 mg) (see abstract# 3010).

It would have been obvious to one of ordinary skill in the art at the time of the invention to treat deep venous thromboses in a patient by administering rivaroxaban as disclosed by the patented claims using the administration guidelines and tablets taught by Kubitza et al.[1] and Kubitza et al.[2] One of ordinary skill in the art would have been motivated to administer rivaroxaban for 5 consecutive days as taught by Kubitza et al.[1] in order to effectively treat deep vein thromboses. One of ordinary skill in the art would have been motivated to administer rivaroxaban once daily using the rapid release tablet Kubitza et al.[2] in order to provide patient convenience and compliance. One of ordinary skill in the art would have had a reasonable expectation of success in treating deep venous thromboses in a patient by administering rivaroxaban as disclosed by the patented claims using the administration guidelines and tablets taught by Kubitza et al.[1] and Kubitza et al.[2] because rivaroxaban is known to treat deep venous thromboses, and Kubitza et al.[1] and Kubitza et al.[2] teach administration guidelines for rivaroxaban that are safe and tolerable for patients.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which

> said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 1, 4, 5, 11, and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Straub et al. (US 2003/0156310 A1) in view of Kubitza et al.[1] ("Multiple dose escalation study investigating the pharmacodynamics, safety, and pharmacokinetics of BAY 59-7939 an oral, direct Factor Xa inhibitor in healthy male subjects," *Blood*, Vol. 102:11 16 Nov. 2003, pgs 811a - cited on IDS) and

Kubitza et al.[2] (ABSTRACT 2010, "Single Dose escalation study investigating the pharmacodynamics, safety, and pharmacokinetics of BAY 59-7939 an oral, direct Factor Xa inhibitor in healthy male subjects," *Blood*, Vol. 102:11, 16 Nov. 2003, page 813a - cited on IDS).

The instant claims are directed to methods of treating deep vein thromboses comprising administering 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-mopholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide (rivaroxaban) no more than once daily for at least five consecutive days in a rapid-release oral dosage form to a patient in need thereof, wherein said inhibitor has a plasma concentration half-life of 10 hours or less when orally administered to a human patient.

Straub et al. teach oxazolidinone derivatives for the treatment of thromboembolic disorders including deep venous thromboses (see abstract; pages 1-2, sections [009]--[0010]; page 17, sections [0392]-[0393]; page 74, claim 10). Straub et al. teach 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-mopholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide (rivaroxaban) as preferred compound (see page 6, section [0145]; page 26, Example 44). Straub et al. teach oral administration is preferred, wherein oral formulations include tablets as claimed in the instant claim 5 (see page 15, sections [0366]-[0367]).

Straub et al. do not teach administering 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-mopholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide (rivaroxaban) once daily for at least five consecutive days. Straub et al. do not

teach the plasma concentration half-life in a human patient. Straub et al. do not teach a rapid release tablet as claimed in the instant claim 5.

Kubitza et al.[1] teach administering 5 mg of BAY 59-7939 (rivaroxaban) once daily to male subjects on day 0 and days 4-8 (i.e. five consecutive days) (see page 811a, subjects and methods).

Kubitza et al.[2] teach administering 1.25 mg to 80 mg of BAY 59-7939 (rivaroxaban) under fasting conditions as a tablet to men, wherein BAY 59-7939 showed rapid onset of action (i.e. rapid release). Kubitza et al. also teach the plasma concentration half-life of the tablet containing BAY 59-7939 was observed 2 hours after administration. Kubitza et al. further teach BAY 59-7939 is safe and well-tolerated across a wide range of oral doses (1.25 mg to 80 mg) (see abstract# 3010).

It would have been obvious to one of ordinary skill in the art at the time of the invention to treat deep venous thromboses in a patient by administering rivaroxaban as taught by Straub et al. using the administration guidelines and tablets taught by Kubitza et al.[1] and Kubitza et al.[2] One of ordinary skill in the art would have been motivated to administer rivaroxaban for 5 consecutive days as taught by Kubitza et al.[1] in order to effectively treat deep vein thromboses. One of ordinary skill in the art would have been motivated to administer rivaroxaban once daily using the rapid release tablet Kubitza et al.[2] in order to provide patient convenience and compliance. One of ordinary skill in the art would have had a reasonable expectation of success in treating deep venous thromboses in a patient by administering rivaroxaban as taught by Straub et al. using the

administration guidelines and tablets taught by Kubitza et al.[1] and Kubitza et al.[2] because rivaroxaban is known to treat deep venous thromboses, and Kubitza et al.[1] and Kubitza et al.[2] teach administration guidelines for rivaroxaban that are safe and tolerable for patients.

Thus, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art.

NEW REJECTIONS

15. In light of Applicant's amendments to claims 1 and 5 and the addition of new claim 18, the following rejections have been newly added:

Claim Rejections - 35 USC § 112

16. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 4, 5, 11, and 18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "no more than once daily…oral dosage form or forms" in claims 1 and 5 renders the claims indefinite because it is unclear if the composition is being administered once or multiple times.

Claims 4, 11, and 18 are rejected for being dependent on a rejected base claim. For examination purposes and in the interest of compact prosecution, the recitation of "or forms" will be ignored.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Correspondence

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jody L. Karol whose telephone number is (571)270-3283. The examiner can normally be reached on 8:30 am - 5:00 pm Mon-Fri EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Jody L. Karol/

Examiner, Art Unit 1627

/SREENI PADMANABHAN/
Supervisory Patent Examiner, Art Unit 1627

PTO/SB/08b (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	11/883,218-Conf. #9960
Filing Date	July 16, 2008
First Named Inventor	Frank Misselwitz
Art Unit	1627
Examiner Name	Jody Lynn Karol
Attorney Docket Number	11987-00042-US

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	CA	BREITENBACH, J. Feste Loesungen durch Schmelzextrusion - ein integriertes Herstellkonzept. Pharmazie in unserer Zeit 29 (2000), 46-49.	
	CB	Pschyrembel, Klinisches Worterbuch, 257. Auflage, 1994, Walter de Gruyter Verlag, p. 610, Stichwort "Heparin."	
	CC	Pschyrembel, Klinisches Worterbuch, 257. Auflage, 1994, Walter de Gruyter Verlag, p. 292, Stichwort "Cumarinderivate."	
	CD	Pschyrembel, Klinisches Worterbuch, 257. Auflage, 1994, Walter de Gruyter Verlag, p. 199-200, Stichwort "Blutgerinnung."	
	CE	Rompp Lexikon Chemie, Ver. 1.5, 1998, Georg Thieme Verlag Stuttgart, Stichwort "Heparin."	
	CF	Rompp Lexikon Chemie, Ver. 1.5, 1998, Georg Thieme Verlag Stuttgart, Stichwort "Blutgerinnung" Lubert Stryer, Biochemie, Spektrum der Wissenschaft Verlagsgesellschaft mbH Heidelberg, 1990, p. 259.	

Examiner Signature	/Jody Karol/	Date Considered	09/08/2011

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11883218	MISSELWITZ ET AL.
	Examiner	Art Unit
	JODY KAROL	1627

SEARCHED			
Class	Subclass	Date	Examiner
514	230.8; 236.8 (see attached)	3/9/2011	JLK
	updated (see attached)	9/8/2011	JLK

SEARCH NOTES		
Search Notes	Date	Examiner
Inventor Search in EAST/PALM	3/9/2011	JLK
EAST Keyword Search (see attached)	3/9/2011	JLK
STIC Search (see attached)	2/17/2011	JLK
STN Search (see attached)	3/9/2011	JLK
Inventor and EAST Search updated (see attached)	9/8/2011	JLK

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	39	(Misslewitz, Frank).in. or (Kubitza, Dagmar).in. or (Park, Son-Mi).in. or (Wehling, Klaus).in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2011/09/08 20:28
L2	135	BAY 59-7939	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2011/09/08 20:28
L3	289	rivaroxaban$3	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2011/09/08 20:28
L4	9225	(deep vein thrombos$2) or (deep venous thrombos$2)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2011/09/08 20:28
L5	1416	L4 and (Xa near3 inhibitor)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2011/09/08 20:28
L6	42	L4 and (direct factor Xa inhibitor)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2011/09/08 20:28
L7	56	L4 and ($thiophenecarboxamide)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2011/09/08 20:28
L8	242	514/230.8.ccls.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2011/09/08 20:28
L9	621	514/236.8.ccls.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2011/09/08 20:28
L10	62	L4 and (L8 or L9)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2011/09/08 20:28

EAST Search History (Interference)

<This search history is empty>

9/8/2011 8:30:36 PM
C:\Users\jkarol\Documents\EAST\Workspaces\11883218 - Prevention and Method of Treatment of Thromboembolic Disorders.wsp

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11883218	MISSELWITZ ET AL.
	Examiner	**Art Unit**
	Jody L Karol	1627

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	11/02/2010	03/09/2011	09/08/2011						
	1	÷	✓	✓						
	2	÷	✓	-						
	3	÷	N	-						
	4	÷	✓	✓						
	5	÷	✓	✓						
	6	÷	✓	-						
	7	÷	N	N						
	8	÷	N	N						
	9		✓	N						
	10		✓	-						
	11		✓	✓						
	12		✓	-						
	13		✓	-						
	14		✓	-						
	15			N						
	16			N						
	17			N						
	18			✓						
	19			N						

Docket No.: 11987-00042-US
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Frank Misselwitz et al.

Application No.: 11/883,218 | Confirmation No.: 9960

Filed: July 27, 2007 | Art Unit: 1627

For: PREVENTION AND TREATMENT OF THROMBOEMBOLIC DISORDERS | Examiner: Jody Lynn Karol

RESPONSE TO NON FINAL OFFICE ACTION

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

INTRODUCTORY COMMENTS

Applicants respond to the Office Action mailed March 17, 2011 as follows:

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 4 of this paper.

AMENDMENTS TO THE CLAIMS

1. (Currently amended) A method of treating a thromboembolic disorder comprising administering a direct factor Xa inhibitor **that is 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide** no more than once daily for at least five consecutive days in **[an] a rapid-release** oral dosage form **or forms** to a patient in need thereof, wherein said inhibitor has a plasma concentration half life of 10 hours or less when orally administered to a human patient.

2. (Cancelled).

3. (Cancelled).

4. (Previously presented) The method of claim 1, wherein the thromboembolic disorder is ST Segment Elevation Myocardial Infarction (STEMI), Non ST Segment Elevation Myocardial Infarction (NSTEMI), unstable angina, reocclusion after angioplasty or aortocoronary bypass, pulmonary embolisms, deep vein thromboses or stroke.

5. (Currently amended) The method of claim 1, wherein the oral dosage form **or forms** is a rapid-release tablet.

6. (Cancelled)

7. (Withdrawn) A packaged pharmaceutical composition comprising a container containing a rapid-release tablet comprising 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide, said container furthermore containing instructions for using said rapid-release tablet to treat a thromboembolic disorder.

8. (Withdrawn) The packaged pharmaceutical composition of claim 7, comprising a container containing a rapid-release tablet comprising 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide, said

container furthermore containing instructions for administering said rapid-release tablet at a frequency of once daily.

9. (Currently amended) The method of ~~claim 2~~ **claim 1**, wherein the thromboembolic disorder is ST Segment Elevation Myocardial Infarction (STEMI)~~, Non ST Segment Elevation Myocardial Infarction (NSTEMI), unstable angina, reocclusion after angioplasty or aortocoronary bypass, pulmonary embolisms, deep vein thromboses or stroke~~.

10. (Cancelled)

11. (Currently amended) The method of claim 4, wherein the ~~oral dosage form is a rapid-release tablet~~ **thromboembolic disorder is Non ST Segment Elevation Myocardial Infarction (NSTEMI).**

12-14 (Cancelled).

15. (New) The method of claim 1, wherein the thromboembolic disorder is unstable angina.

16. (New) The method of claim 1, wherein the thromboembolic disorder is reocclusion after angioplasty or aortocoronary bypass.

17. (New) The method of claim 1, wherein the thromboembolic disorder is pulmonary embolisms.

18. (New) The method of claim 1, wherein the thromboembolic disorder is deep vein thromboses.

19. (New) The method of claim 1, wherein the thromboembolic disorder is stroke.

REMARKS

After entry of this Amendment, claims 1, 4, 5, 7-9, 11, and 15-19 are pending, with claims 7 and 8 being withdrawn. The amendments to the claims are made without prejudice or disclaimer to presenting the cancelled subject matter in subsequent applications. Support for the claim amendments is found *inter alia* in the original claims and specification, such as for example in original claims 5 and 6 (amendments to claim 1), original claim 4 (new claims 15-19 and amendments to claims 9 and 11), page 10 lines 18-20 and page 10 lines 3-6 (amendments to claims 1 and 5). No new matter has been added.

The Invention

The direct factor Xa inhibitor 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide, also known as rivaroxaban, was a known, orally administrable medicament for the treatment and prevention of thromboembolic disorders. It was shown to have a plasma half-life of 4-6 hours in humans. Specification, page 4 lines 4-9, citing D. Kubitza et al., Multiple Dose Escalation Study Investigating the Pharmacokinetics, Safety, and Pharmacokinetics of Bayer 59-7939 an Oral, Direct Factor Xa Inhibitor in Healthy Male Subjects, Blood 2003, 102, Abstract 3004, which is referred to as "Kubitza et al.[2]" in the Office Action.

When a drug is dosed in no more than a therapeutically active amount (which is desired to minimize side effects), the drug must be given approximately every half life. Page 3 lines 4-6. Surprisingly, Applicants found that once daily oral administration of rivaroxaban, despite its 4-6 hour half life, demonstrated efficacy similar to twice daily dosing. Page 3 lines 15-18.

Double Patenting Rejection

Claims 1, 2, 4-6 and 9-14 stand rejected under the doctrine of double patenting as not patentably distinct from claims 13, 24 and 30 of US Patent 7,157,456. Applicants respectfully disagree. The claims from the '456 patent disclose methods of treatment using rivaroxaban, the compound of the present claims. However, in contrast to the present claims, the patented claims

do not disclose the once daily dosing in a rapid-release oral dosage form or forms. The present invention concerns this novel and surprising discovery that rivaroxaban can be efficacious with only once daily dosing for at least five days with a rapid-release oral dosage form. As discussed above, conventional wisdom (as shown in the articles cited on page 3 of the specification) would have led one of ordinary skill in the art to believe that efficacy of a drug with a half life of 10 hours or less required more frequent dosing, such as twice daily dosing.

Because this element of the dosage frequency in a rapid-release oral dosage form was not disclosed in the patented claims, withdrawal of the double patenting rejection is urged.

Claims 1, 2, 4-6 and 9-14 stand rejected under the doctrine of double patenting as not patentably distinct from claims 1-6 and 17-21 of US Patent 7,592,339 (mistakenly identified as 7,592,399 in the Office Action). Similarly to the rejection above, the patented claims of the '339 patent also recite methods of inhibition of thrombus formation or treating disorders using rivaroxaban but do not recite the dosage frequency or dosage form. Therefore, for the same reasons presented regarding the double patenting rejection over the '456 patent claims, the double patenting rejection based on the '339 patent should be reconsidered and withdrawn.

The Office Action also discusses that a filing of a statement of common ownership for US Patents 7,157,456 and 7,592,399 and US Application No. 11/317,720 would preclude a rejection under 35 USC 103 (c) if such references were only prior art pursuant to section 102 (e), (f) or (g). Applicants do not choose to make such a declaration at this time.

Nonstatutory Double Patenting Rejection

Claims 1, 2, 4-6 and 9-14 stand rejected on the grounds of nonstatutory obviousness-type double patenting based on the same claims of the '456 and '339 patents discussed above, now in combination with Kubitza et al.[1] ("Multiple Dose Escalation Study Investigating the Pharmacodynamics, Safety and Pharmacokinetics of BAY 59-7939 an Oral, Direct Factor Xa Inhibitor in Healthy Male Subjects," Blood, vol. 102:11 (16 Nov. 2003), p. 811a) and Kubitza et al.[2] We respectfully disagree.

As discussed above, the patented claims do not disclose the presently claimed once daily dosage for at least five consecutive days of a rapid-release oral dosage form or forms. Kubitza et al.[1] and Kubitza et al.[2] do not provide the missing teaching. Kubitza et al.[1] and Kubitza et al.[2] report pharmacokinetic studies of rivaroxaban in ***healthy*** subjects. Neither reference discloses dosages required for efficacy in patients suffering from, or at risk from, a thromboembolic disorder. Furthermore, neither Kubitza et al.[1] nor Kubitza et al.[2] disclose that an efficacious dose would be a rapid-release dosage oral dosage form or forms administered once daily, as in the presently claimed methods.

The Office Action alleges that one of ordinary skill in the art would have been motivated to administer rivaroxaban for five consecutive days as taught by Kubitza et al.[1] to effectively treat deep vein thromboses. The Office Action also alleges that one of ordinary skill in the art would have been motivated to administer rivaroxaban once daily using the rapid release tablet of Kubitza et al.[2] to provide patient convenience and compliance.

However, to the contrary, the person of ordinary skill in the art looking for an effective dose of rivaroxaban would have looked at half life and pharmacokinetics of rivaroxaban. These considerations lead away from once daily dosing with a rapid-release oral dosage form. As discussed above, it was well known to a person of ordinary skill in the art that a drug having a half life of ten hours or less usually cannot be efficacious with once daily oral administration of a rapid-release form. Accordingly, one of ordinary skill in the art would not have been motivated to administer rivaroxaban only once daily and in a rapid-release dosage form because successful therapy was not expected.

It had been demonstrated by preclinical investigations that the k_i value for free factor Xa is 0.4 nM, which would be equivalent to a plasma concentration of approximately 0.17 microgram/L of unbound rivaroxaban. The administration of 10 mg rivaroxaban once daily in phase II studies resulted in free plasma concentrations at trough of 0.91 microgram/L, which is approximately five-fold higher than the k_i value for free factor Xa. Therefore, the offset of action can be described by the elimination of rivaroxaban from plasma, which, based on an elimination half life of 11-13 hours, can be assumed to be between 48-72 hours after the last

intake of rivaroxaban 10 mg rapid release tablet. This supports the once-daily dosing regimen for rivaroxaban.

The data mentioned on page 13 table 1-1 and page 13 lines 2 to 5 clearly demonstrates the efficacy of once daily ("od") administration of rivaroxaban. Also, the data shown on pages and 14 in tables 1-1 and 1-2 demonstrates fewer occurrences of composite endpoint events, i.e., fewer cases of deep vein thrombosis (DVT), pulmonary embolisms (PE) or death compared to untreated conditions, with the once daily ("od") dosing, and in the range of standard therapy (see 30 mg dose od and twice daily ("bid")). Furthermore, the od administration is surprisingly perfectly in line with twice daily (bid) administration.

By comparing the total daily doses administered it could be demonstrated also that after once daily administration efficacy, on the one hand, and major bleeding, an expected side effect, on the other hand, match well the expected effects after twice daily administration. Page 4 lines 20 to 22. The data present on page 14 in table 1-2 and page 14 lines 3-5 clearly demonstrate the safety of once daily administration of rivaroxaban (see 30 mg dose od and bid). The occurrence of any major bleeding events is low, approximately in the range of standard therapy, and again perfectly in line with results from bid administration.

The Office Action alleges that a person of ordinary skill in the art would have had a reasonable expectation of success with once daily rivaroxaban administration for five consecutive days because rivaroxaban was known to treat venous thromboses, and Kubitza et al.[1] and Kubitza et al.[2] disclose safe and tolerable rivaroxaban dosages. However, as discussed above, the person of ordinary skill would have looked at the half life of rivaroxaban and expected that if a rapid-release oral dosage form was administered, it must be administered more frequently than once daily. Accordingly, for the reasons stated above, the cited references would not have provided one of ordinary skill in the art with a reasonable expectation of successful therapy with the recited dosage form and regimen.

Accordingly, for these reasons, Applicants respectfully request that the obviousness double patenting rejection be withdrawn.

Rejections under 35 USC § 112

Claims 1, 2, 4, 5, and 9-11 stand rejected under 35 USC § 112, first paragraph as not enabled by the specification. Applicants respectfully disagree. However, to expedite prosecution, the claims are amended to recite methods of administering rivaroxaban, which the Examiner indicated was enabled. Accordingly, reconsideration and withdrawal of this rejection is requested.

Rejections under 35 USC § 103

Claims 1, 2, 4-6 and 9-14 are rejected as obvious over Straub et al. (US Application Pub. 2003/0153610)[1] in view of Kubitza et al.[1] and Kubitza et al.[2] We respectfully disagree.

As the Office Action admits, Straub et al. does not teach administering rivaroxaban once daily for at least five consecutive days, or the plasma concentration half life of rivaroxaban. The Patent Office has also not found a teaching in Straub et al. of a rapid-release tablet.

The Office Action relies on Kubitza et al.[1] and Kubitza et al.[2] for teaching administering 5 mg of rivaroxaban once daily for 4-8 days, dosing rivaroxaban to men with rapid onset of action, a 2-hour half life of a rivaroxaban tablet, and safe and well-tolerated dosages across a range of oral dosages of 1.25 mg to 80 mg. Yet as discussed above in the discussion of the double patenting rejection, Kubitza et al.[1] and Kubitza et al.[2] disclose administration to healthy subjects, and do not disclose that once daily oral dosaging of a rapid-release form of rivaroxaban for at least five days would be efficacious.

Furthermore, for the same reasons discussed above, the person of ordinary skill in the art would not have been motivated to modify the dosages taught for once daily administration of a rapid-release form, nor would the person have expected such a treatment regimen to be successful because of the half life of rivaroxaban. Contrary to the conclusions in the Office

[1] Straub et al. is the published application that resulted in the granted '456 patent discussed in the double patenting rejections above. Also, for clarity, the Office Action transposes two numbers in the Straub et al. publication number, US 2003/015<u>63</u>10, but the correction is obvious so we address the application 2003/015<u>36</u>10.

Action, a reasonable expectation of success with the claimed dosing regimen cannot be found in the Kubitza et al.[1] and Kubitza et al.[2] disclosures of safe and tolerable dosages when the art accepted the primacy of pharmacokinetic values such as half life in determining a likely successful oral dosage regimen.

Thus, for the same reasons provided above regarding the double patenting rejections involving Kubitza et al.[1] and Kubitza et al.[2], reconsideration and withdrawal of the obviousness rejection is respectfully requested.

CONCLUSION

Applicant believes no fee is due with this paper. However, if a fee is due, please charge our Deposit Account No. 03-2775, under Order No. 11987-00042-US from which the undersigned is authorized to draw.

Dated: June 17, 2011

Respectfully submitted,

#4,247,605

Christine M. Hansen
Registration No.: 40,634
CONNOLLY BOVE LODGE & HUTZ LLP
1007 North Orange Street
P. O. Box 2207
Wilmington, Delaware 19899-2207
(302) 658-9141
Attorney for Applicant

Docket No.: 11987-00042-US
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Frank Misselwitz et al.

Application No.: 11/883,218 Confirmation No.: 9960

Filed: July 16, 2008 Art Unit: 1627

For: PREVENTION AND TREATMENT OF THROMBOEMBOLIC DISORDERS Examiner: Jody Lynn Karol

INFORMATION DISCLOSURE STATEMENT (IDS)

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Pursuant to 37 CFR 1.56, 1.97 and 1.98, the attention of the Patent and Trademark Office is hereby directed to the references listed on the attached PTO/SB/08. It is respectfully requested that the information be expressly considered during the prosecution of this application, and that the references be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

This Information Disclosure Statement is filed more than three months after the U.S. filing date, OR more than three months after the date of entry of the national stage of a PCT application, AND after the mailing date of the first Office Action on the merits, whichever occurs first, but before the mailing date of any of a Final Office Action, a Notice of Allowance (37 CFR 1.97(c)) or an action that otherwise closes prosecution in the application.

In accordance with 37 CFR 1.98(a)(2)(ii), Applicant has not submitted copies of U.S. patents and U.S. patent applications. Applicant submits herewith copies of foreign patents and non-patent literature in accordance with 37 CFR 1.98(a)(2).

In accordance with 37 CFR 1.97(g), the filing of this Information Disclosure Statement shall not be construed to mean that a search has been made or that no other material information as defined in 37 CFR 1.56(a) exists. In accordance with 37 CFR 1.97(h), the filing of this Information Disclosure Statement shall not be construed to be an admission that any patent, publication or other information referred to therein is "prior art" for this invention unless specifically designated as such.

The German language reference Breitenbach, J., "Feste Lösungen durch Schmelzextrusion – ein integriertes Herstellkonzept" [translated roughly as – Solid dosages through melt extrusion: an integrated production process --] Pharmazie in unserer Zeit 29 (2000), 46-49 concerns a method for amorphisation of an active ingredient such as rivaroxaban in which an active ingredient is melted together with one or more suitable excipients. It is referred to on page 4 line 30 to page 5 line 2 of US Application Ser. No 11/317720, which application concerns rivaroxaban like the present claims.

The remaining German language entries concern the clinical dictionary definitions. The entries for Pschyrembel, Klinisches Worterbuch "Blutgerinnung" and Rompp Lexikon Chemie for "Blutgerinnung" (meaning blood coagulation) have relevance as disclosed in paragraph [0004] of US Patent App. Pub. 20030153610: "These thromboembolic disorders are the most frequent cause of morbidity and mortality in most industrialized countries (Pschyrembel, Klinisches Worterbuch [clinical dictionary], 257.sup.th edition, 1994, Walter de Gruyter Verlag, page 199 ff., entry "Blutgerinnung" [blood coagulation]; Rompp Lexikon Chemie, Version 1.5, 1998, Georg Thieme Verlag Stuttgart, entry "Blutgerinnung"; Lubert Stryer, Biochemie [biochemistry], Spektrum der Wissenschaft Verlagsgesellschaft mbH Heidelberg, 1990, page 259 ff.)." The entries for Pschyrembel, Klinisches Worterbuch "Heparin," and Rompp Lexikon Chemie for "Heparin" have relevance as disclosed in paragraph [0006] of US Patent App. Pub. 20030153610: "In the therapy and prophylaxis of thromboembolic disorders, use is firstly made of heparin, which is administered parenterally or subcutaneously. Owing to more favourable pharmacokinetic properties, preference is nowadays more and more given to low-molecular-weight heparin; however, even with low-molecular-weight heparin, it is not possible to avoid the

known disadvantages described below, which are involved in heparin therapy. Thus, heparin is ineffective when administered orally and has a relatively short half-life. Since heparin inhibits a plurality of factors of the blood coagulation cascade at the same time, the action is nonselective. Moreover, there is a high risk of bleeding; in particular, brain haemorrhages and gastrointestinal bleeding may occur, which may result in thrombopenia, drug-induced alopecia or osteoporosis (Pschyrembel, Klinisches Worterbuch, 257.sup.th edition, 1994, Walter de Gruyter Verlag, page 610, entry "Heparin"; Rompp Lexikon Chemie, Version 1.5, 1998, Georg Thieme Verlag Stuttgart, entry "Heparin")."

The reference Pschyrembel, Klinisches Worterbuch "Cumarinderivate," (coumarin derivatives) has relevance as disclosed in paragraph [0007] of US Patent App. Pub. 20030153610: "A second class of anticoagulants are the vitamin K antagonists. These include, for example, 1,3-indanediones, and especially compounds such as warfarin, phenprocoumon, dicumarol and other coumarin derivatives which inhibit the synthesis of various products of certain vitamin K-dependent coagulation factors in the liver in a non-selective manner. Owing to the mechanism of action, however, the onset of the action is very slow (latency to the onset of action 36 to 48 hours). It is possible to administer the compounds orally; however, owing to the high risk of bleeding and the narrow therapeutic index, a time-consuming individual adjustment and monitoring of the patient are required. Moreover, other adverse effects, such as gastrointestinal disturbances, hair loss and skin necroses, have been described (Pschyrembel, Klinisches Worterbuch, 257.sup.th edition, 1994, Walter de Gruyter Verlag, page 292 ff., entry "coumarin derivatives"; Ullmann's Encyclopedia of Industrial Chemistry, 5.sup.th edition, VCH Verlagsgesellschaft, Weinheim, 1985-1996, entry "vitamin K")."

It is submitted that the Information Disclosure Statement is in compliance with 37 CFR 1.98 and the Examiner is respectfully requested to consider the listed references.

Please charge our Credit Card in the amount of $180.00 covering the fee set forth in 37 CFR 1.17(p). The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in

this application by this firm) to our Deposit Account No. 03-2775, under Order No. 11987-00042-US.

Dated: June 17, 2011

Respectfully submitted,

Electronic signature: /Christine M. Hansen/
Christine M. Hansen
Registration No.: 40,634
CONNOLLY BOVE LODGE & HUTZ LLP
1007 North Orange Street
P. O. Box 2207
Wilmington, Delaware 19899-2207
(302) 658-9141
(302) 658-5614 (Fax)
Attorney for Applicant

#4359506

PTO/SB/08b (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	11/883,218-Conf. #9960
Filing Date	July 16, 2008
First Named Inventor	Frank Misselwitz
Art Unit	1627
Examiner Name	Jody Lynn Karol
Attorney Docket Number	11987-00042-US

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	CA	BREITENBACH, J. Feste Loesungen durch Schmelzextrusion - ein integriertes Herstellkonzept. Pharmazie in unserer Zeit 29 (2000), 46-49.	
	CB	Pschyrembel, Klinisches Worterbuch, 257. Auflage, 1994, Walter de Gruyter Verlag, p. 610, Stichwort "Heparin."	
	CC	Pschyrembel, Klinisches Worterbuch, 257. Auflage, 1994, Walter de Gruyter Verlag, p. 292, Stichwort "Cumarinderivate."	
	CD	Pschyrembel, Klinisches Worterbuch, 257. Auflage, 1994, Walter de Gruyter Verlag, p. 199-200, Stichwort "Blutgerinnung."	
	CE	Rompp Lexikon Chemie, Ver. 1.5, 1998, Georg Thieme Verlag Stuttgart, Stichwort "Heparin."	
	CF	Rompp Lexikon Chemie, Ver. 1.5, 1998, Georg Thieme Verlag Stuttgart, Stichwort "Blutgerrinung" Lubert Stryer, Biochemie, Spektrum der Wissenschaft Verlagsgesellschaft mbH Heidelberg, 1990, p. 259.	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

Electronic Patent Application Fee Transmittal

Application Number:	11883218
Filing Date:	16-Jul-2008
Title of Invention:	Prevention and Treatment of Thromboembolic Disorders
First Named Inventor/Applicant Name:	Frank Misselwitz
Filer:	Christine Hansen/Sara Maloney
Attorney Docket Number:	11987-00042

Filed as Large Entity

U.S. National Stage under 35 USC 371 Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**180**

Electronic Acknowledgement Receipt

EFS ID:	10333199
Application Number:	11883218
International Application Number:	
Confirmation Number:	9960
Title of Invention:	Prevention and Treatment of Thromboembolic Disorders
First Named Inventor/Applicant Name:	Frank Misselwitz
Customer Number:	23416
Filer:	Christine Hansen/Sara Maloney
Filer Authorized By:	Christine Hansen
Attorney Docket Number:	11987-00042
Receipt Date:	17-JUN-2011
Filing Date:	16-JUL-2008
Time Stamp:	16:36:29
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$180
RAM confirmation Number	3353
Deposit Account	
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1		Response_Non_Final_Office_Action.pdf	456816 c04446d4aeb1c48807e8bde4dc624d1f716445c3	yes	9

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Claims	2	3
	Applicant Arguments/Remarks Made in an Amendment	4	9

Warnings:

Information:

2	Transmittal Letter	IDS_Letter2.pdf	192659 4c14a4398bab12a784bf0653f6f8b95306c862d0	no	4

Warnings:

Information:

3	Information Disclosure Statement (IDS) Form (SB08)	IDS_Filed2.pdf	88002 ec5e2a7d50b33bfa4b09a13e97d87fff49c9d185	no	1

Warnings:

Information:

This is not an USPTO supplied IDS fillable form

4	Non Patent Literature	Breitenbach_Jorg.pdf	694118 988750b34c8a0b8377bc21015696123d3c49d908	no	4

Warnings:

Information:

5	Non Patent Literature	PSCHYREMBEL_610.pdf	89217 7b597ada2c84ac05f161b810908faef31e1cb873	no	2

Warnings:

Information:

6	Non Patent Literature	PSCHYREMBEL_292_293.pdf	163149 8873f0e4e157b9ebef498a59dd8d372d8969f07e	no	3

Warnings:

Information:

7	Non Patent Literature	PSCHYREMBEL_199_200.pdf	152533 1f10e122d85c7a664c03924cbbdffeaa0e47f02c	no	3

Warnings:

Information:

8	Non Patent Literature	ROMPP_HEPARIN.pdf	77094 f170f25ddd336e08bd2a18adc37b21c3b940ca67	no	2
Warnings:					
Information:					
9	Non Patent Literature	ROMPP_BLUTGERINNUNG.pdf	127982 208c3ce58fe84e5ce265170f0533a7abe5a916dc	no	2
Warnings:					
Information:					
10	Fee Worksheet (SB06)	fee-info.pdf	30051 a3787c930beb2ce65cfa1c0d6ba46534e90eed25	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	2071621	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 11/883,218	Filing Date 07/16/2008	☐ To be Mailed

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☐		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	06/17/2011	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 12	Minus	** 20	= 0	X $ =		OR	X $52=	0
	Independent (37 CFR 1.16(h))	* 2	Minus	***3	= 0	X $ =		OR	X $220=	0
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/NICOLE LOVE-HENSLEY/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/883,218	07/16/2008	Frank Misselwitz	11987-00042	9960

23416 7590 03/17/2011
CONNOLLY BOVE LODGE & HUTZ, LLP
P O BOX 2207
WILMINGTON, DE 19899

EXAMINER	
KAROL, JODY LYNN	

ART UNIT	PAPER NUMBER
1627	

MAIL DATE	DELIVERY MODE
03/17/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	11/883,218	MISSELWITZ ET AL.	
	Examiner	Art Unit	
	JODY KAROL	1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 December 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) *3,7 and 8* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-6 and 9-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/27/2007; 5/21/2008; 10/23/2008, and 6/5/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's Amendments and response to the Election/Restriction Requirement filed on 12/10/2010 have been received and entered into the Application. Claims 4-6 are amended. Claims 9-14 are newly added. Claims 1-14 are pending.

Election/Restrictions

1. Applicant's election **with** traverse of Group II, claims 1-2 and 4-6 (in part) directed to a method of treating a thromboembolic disorder comprising administering a direct factor Xa inhibitor no more than once daily for at least five consecutive days in an oral dosage form to a patient in need thereof and the species election **with** traverse of (1) deep vein thrombosis as the species of thromboembolic disorder and (2) 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-mopholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide as the species of direct factor Xa inhibitors in the reply filed on 12/10/2010 is acknowledged.

Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). It is noted that amended claims 4-6 in full and new claims 9-14 are considered to correspond to Group II.

The requirement is still deemed proper and is therefore made FINAL.

Claims 3, 7, and 8 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or

linking claim. Accordingly, claims 1, 2, 4-6, and 9-12 are examined on the merits herein, and prior art is applied in so much as it reads on the elected species.

Priority

2. This Application is a 371 of PCT/EP/00431 filed on 1/19/2006 which claims foreign priority to Application No. 05001893.6 filed with the European Patent Office on 1/31/2005.

Information Disclosure Statement

3. The information disclosure statements (IDS) filed on 7/27/2007; 5/21/2008; 10/23/2008; and 6/5/2009 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements have been considered. However, NPL reference CG3, CH3, CJ3, CK3, and CV3 on the 10/23/2008 IDS have not been considered because English language translation of the documents were not provided, and their relevance to the application has not been indicated.

Double Patenting

4. Claims 1, 2, 4-6, and 9-14 are directed to an invention not patentably distinct from claims 13, 24, and 30 of commonly assigned US 7,157,456 B2. Specifically, the instant claims and the patented claims are both directed to methods of treating thromboembolic disorders comprising administering 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-

oxo-4-mopholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide (rivaroxaban).

5. Claims 1, 2, 4-6, and 9-14 are directed to an invention not patentably distinct from claims 1-6 and 17-21 of commonly assigned US 7,592,399 B2. Specifically, the instant claims and the patented claims are both directed to methods of treating thromboembolic disorders comprising administering 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-mopholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide (rivaroxaban).

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned US 7,157,456 B2, US 7,592,399 B2, and US Application No. 11/317,720 discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon

the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

Nonstatutory Double Patenting

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 1, 2, 4-6, and 9-14 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 13, 24, and 30 of U.S. Patent No. 7,157,456 B2 in view of Kubitza et al.[1] ("Multiple dose escalation study investigating the pharmacodynamics, safety, and pharmacokinetics of BAY 59-7939 an oral, direct Factor Xa inhibitor in healthy male subjects," *Blood*, Vol. 102:11 16 Nov. 2003, pgs 811a - cited on IDS) and Kubitza et al.[2] (ABSTRACT 2010, "Single Dose escalation study investigating the pharmacodynamics, safety, and pharmacokinetics of

BAY 59-7939 an oral, direct Factor Xa inhibitor in healthy male subjects," *Blood*, Vol. 102:11, 16 Nov. 2003, page 813a - cited on IDS).

Although the conflicting claims are not identical, they are not patentably distinct from each other because they are both directed to methods of treating thromboembolic disorders comprising administering 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-mopholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide (rivaroxaban).

The patented claims do not teach administering 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-mopholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide (rivaroxaban) once daily for at least five consecutive days. The patented claims do not teach the plasma concentration half life in a human patient. The patented claims do not teach a rapid release tablet as claimed in the instant claims 5, 10, 11, and 14.

Kubitza et al.[1] teach administering 5 mg of BAY 59-7939 (rivaroxaban) once daily to male subjects on day 0 and days 4-8 (i.e. five consecutive days) (see page 811a, subjects and methods).

Kubitza et al.[2] teach administering 1.25 mg to 80 mg of BAY 59-7939 (rivaroxaban) under fasting conditions as a tablet to men, wherein BAY 59-7939 showed rapid onset of action (i.e. rapid release as claimed in the instant claims 5, 10, 11, and 14). Kubitza et al. also teach the plasma concentration half life of the tablet containing BAY 59-7939 was observed 2 hours after administration. Kubitza et al. further teach BAY 59-7939 is safe and well-tolerated across a wide range of oral doses (1.25 mg to 80 mg) (see abstract# 3010).

It would have been obvious to one of ordinary skill in the art at the time of the invention to treat deep venous thromboses in a patient by administering rivaroxaban as disclosed by the patented claims using the administration guidelines and tablets taught by Kubitza et al.[1] and Kubitza et al.[2] One of ordinary skill in the art would have been motivated to administer rivaroxaban for 5 consecutives days as taught by Kubitza et al.[1] in order to effectively treat deep vein thromboses. One of ordinary skill in the art would have been motivated to administer rivaroxaban once daily using the rapid release tablet Kubitza et al.[2] in order to provide patient convenience and compliance. One of ordinary skill in the art would have had a reasonable expectation of success in treating deep venous thromboses in a patient by administering rivaroxaban as disclosed by the patented claims using the administration guidelines and tablets taught by Kubitza et al.[1] and Kubitza et al.[2] because rivaroxaban is known to treat deep venous thromboses, and Kubitza et al.[1] and Kubitza et al.[2] teach administration guidelines for rivaroxaban that are safe and tolerable for patients.

8. Claims 1, 2, 4-6, and 9-14 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6 and 17-21 of U.S. Patent No. 7,592,399 B2 in view of Kubitza et al.[1] ("Multiple dose escalation study investigating the pharmacodynamics, safety, and pharmacokinetics of BAY 59-7939 an oral, direct Factor Xa inhibitor in healthy male subjects," *Blood*, Vol. 102:11 16 Nov. 2003, pgs 811a - cited on IDS) and Kubitza et al.[2] (ABSTRACT 2010, "Single Dose escalation study investigating the pharmacodynamics, safety, and pharmacokinetics of

BAY 59-7939 an oral, direct Factor Xa inhibitor in healthy male subjects," *Blood*, Vol. 102:11, 16 Nov. 2003, page 813a - cited on IDS).

Although the conflicting claims are not identical, they are not patentably distinct from each other because they are both directed to methods of treating thromboembolic disorders comprising administering 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-mopholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide (rivaroxaban)..

The patented claims do not teach administering 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-mopholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide (rivaroxaban) once daily for at least five consecutive days. The patented claims do not teach the plasma concentration half life in a human patient. The patented claims do not teach a rapid release tablet as claimed in the instant claims 5, 10, 11, and 14.

Kubitza et al.[1] teach administering 5 mg of BAY 59-7939 (rivaroxaban) once daily to male subjects on day 0 and days 4-8 (i.e. five consecutive days) (see page 811a, subjects and methods).

Kubitza et al.[2] teach administering 1.25 mg to 80 mg of BAY 59-7939 (rivaroxaban) under fasting conditions as a tablet to men, wherein BAY 59-7939 showed rapid onset of action (i.e. rapid release as claimed in the instant claims 5, 10, 11, and 14). Kubitza et al. also teach the plasma concentration half life of the tablet containing BAY 59-7939 was observed 2 hours after administration. Kubitza et al. further teach BAY 59-7939 is safe and well-tolerated across a wide range of oral doses (1.25 mg to 80 mg) (see abstract# 3010).

It would have been obvious to one of ordinary skill in the art at the time of the invention to treat deep venous thromboses in a patient by administering rivaroxaban as disclosed by the patented claims using the administration guidelines and tablets taught by Kubitza et al.[1] and Kubitza et al.[2] One of ordinary skill in the art would have been motivated to administer rivaroxaban for 5 consecutives days as taught by Kubitza et al.[1] in order to effectively treat deep vein thromboses. One of ordinary skill in the art would have been motivated to administer rivaroxaban once daily using the rapid release tablet Kubitza et al.[2] in order to provide patient convenience and compliance. One of ordinary skill in the art would have had a reasonable expectation of success in treating deep venous thromboses in a patient by administering rivaroxaban as disclosed by the patented claims using the administration guidelines and tablets taught by Kubitza et al.[1] and Kubitza et al.[2] because rivaroxaban is known to treat deep venous thromboses, and Kubitza et al.[1] and Kubitza et al.[2] teach administration guidelines for rivaroxaban that are safe and tolerable for patients.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4, 5, and 9-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a thromboembolic disorder comprising administering 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-

4-mopholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide (rivaroxaban) to a patient in need thereof, does not reasonably provide enablement for a method of treating a thromboembolic disorder comprising administering a direct factor Xa inhibitor to a patient in need thereof, wherein the direct factor Xa inhibitor includes each and every inhibitor known and unknown. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without **undue experimentation** *(United States v. Telectronics, Inc.,* 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is required is not based upon a single factor, but rather is a conclusion reached by weighing many factors. These factors were outlined in *Ex parte Forman,* 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands,* 8 USPQ2d 1400 (Fed. Cir. 1988) and include the following: (1) breadth of the claims; (2) nature of the invention; (3) state of the prior art; (4) amount of direction provided by the inventor; (5) the level of predictability in the art; (6) the existence of working examples; (7) quantity of experimentation needed to make or use the invention based on the content of the disclosure; and (8) relative skill in the art. All of the factors have been considered with regard to the claims, with the most relevant factors discussed below:

(1) The nature of the invention: The instant invention pertains to methods of treating a thromboembolic disorder comprising administering a direct factor Xa inhibitor

no more than once daily for at least five consecutive days in an oral dosage form to a patient in need thereof, wherein said inhibitor has a plasma concentration half life of 10 hours or less when orally administered to a human patient.

(2) The breadth of claims: Claims 1, 2, 4, 5, and 9-11 are directed to methods of treating a thromboembolic disorder comprising administering a direct factor Xa inhibitor no more than once daily for at least five consecutive days in an oral dosage form to a patient in need thereof, wherein said inhibitor has a plasma concentration half life of 10 hours or less when orally administered to a human patient. The treatment of a thromboembolic disorder with each and every compound classified as a direct factor Xa inhibitor, including those inhibitors that are known and yet to be discovered is a very broad claim that is not supported by the instant specification.

(3) The state of the prior art: It is known in the prior art that that inhibitors of factor Xa may be useful as antithrombotic drugs (see Hauptmann et al., "Synthetic Inhibitors of Thrombin and Factor Xa: From Bench to Bedside," *Thrombosis Research*, 93 (1999) pgs 203-241 - cited on IDS). For example, Straub et al. (US 2003/0156310 A1 - cited on IDS) teach substituted oxazolidinone derivatives that inhibit factor Xa and are useful in the treatment of thromboembolic disorders (see abstract; pages 2-3, section [0008]-[0011]; page 74, claim 10). Rivaroxaban is provided as an example (see page 6, section [0145]). However, the prior art also teaches a wide variety of factor Xa inhibitors are known. Moreover, the structures of the inhibitors vary greatly, and include peptide and small molecule inhibitors (see Al Obeidi et al., "Factor Xa inhibitors," *Exp. Opin. Ther. Patents*, (1999) 9(7): pgs 931-953 – cited on IDS). In short, the art

recognizes treating thromboembolic disorders by administering rivaroxaban and recognizes inhibiting factor Xa may be an approach to treating thromboembolic disorders, but does not recognize that each and every inhibitor of direct factor Xa, known and unknown, will treat thromboembolic disorders.

(4) The amount of direction provided by the inventor: There is nothing in the specification that would indicate that administering any direct factor Xa inhibitor would treat a thromboembolic disorder. Examples of direct factor Xa inhibitors are provided on pages 5-8 of the instant specification. Dosage guidelines, dosage forms, and administration guidelines are provided on page 10 of the instant specification.

(5) Predictability of the art: The prior art teaches a link between inhibition of direct factor Xa and the treatment of thromboembolic disorders. However, it is not predictable that all direct factor Xa inhibitors known and yet to be discovered will be useful in the treatment of thromboembolic disorders.

(6) The presence or absence of working examples: Applicant describes a dose guiding study comparing the effects of the direct factor Xa inhibitor rivaroxaban with enoxaparin, wherein rivaroxaban reduced the rates of venous thromboembolism in adult subjects undergoing elective hip replacement compared to enoxaparin (see pages 11-13).

Overall, applicant fails to provide examples indicating that the instant method can treat thromboembolic disorders by administering each and every inhibitor of direct factor Xa. Therefore, the practitioner would turn to trial and error experimentation to

determine which direct factor Xa inhibitors treat thromboembolic disorders, without guidance from the specification or the prior art.

(7) The quantity of experimentation: In order to utilize the methods as claimed, the skilled artisan would be presented with an unpredictable amount of experimentation to determine, for example, which inhibitors of direct factor Xa were effective at treating thromboembolic disorders, and effective dosages for treatment. The number of inhibitors of direct factor Xa, known and not yet discovered is extensive. Consequently, a burdensome amount of research would be required by one of ordinary skill in the art to practice the full scope of methods as instantly claimed.

(8) The relative skill of those in the art: The skill of one of ordinary skill in the art is relatively high, i.e., Ph.D. and M.D. level technology.

In the instant case, an impermissible burden of undue experimentation is necessary to determine which inhibitors of direct factor Xa, known and not yet discovered, are effective in the treatment of thromboembolic disorders. An exhaustive study would have to be conducted with the various inhibitors of direct factor Xa, possibly several times with each study under slightly different conditions. *Genetech,* 108 F.3d at 1366, states that "a patent is not a hunting license. It is not a reward for a search, but compensation for a successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not vague intimations of general ideas that may or may not be workable."

For the above reasons and analysis of the undue experimentation factors, a person skilled in the art would have to engage in undue experimentation to practice the methods of the instant claims with no assurance of success.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1-2, 4-6, 9-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Straub et al. (US 2003/0156310 A1) in view of Kubitza et al.[1] ("Multiple dose escalation study investigating the pharmacodynamics, safety, and pharmacokinetics of BAY 59-7939 an oral, direct Factor Xa inhibitor in healthy male subjects," *Blood*, Vol. 102:11 16 Nov. 2003, pgs 811a - cited on IDS) and Kubitza et al.[2] (ABSTRACT 2010, "Single Dose escalation study investigating the pharmacodynamics, safety, and pharmacokinetics of BAY 59-7939 an oral, direct Factor Xa inhibitor in healthy male subjects," *Blood*, Vol. 102:11, 16 Nov. 2003, page 813a - cited on IDS).

The instant claims are directed to methods of treating deep vein thromboses comprising administering 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-mopholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide (rivaroxaban) no more than once daily for at least five consecutive days in an oral dosage form to a patient in need thereof, wherein said inhibitor has a plasma concentration half life of 10 hours or less when orally administered to a human patient.

Straub et al. teach oxazolidinone derivatives for the treatment of thromboembolic disorders including deep venous thromboses (see abstract; pages 1-2, sections [009]--[0010]; page 17, sections [0392]-[0393]; page 74, claim 10). Straub et al. teach 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-mopholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide (rivaroxaban) as preferred compound (see page 6, section

[0145]; page 26, Example 44). Straub et al. teach oral administration is preferred, wherein oral formulations include tablets (see page 15, sections [0366]-[0367]).

Straub et al. do not teach administering 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-mopholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide (rivaroxaban) once daily for at least five consecutive days. Straub et al. do not teach the plasma concentration half life in a human patient. Straub et al. do not teach a rapid release tablet as claimed in the instant claims 5, 10, 11, and 14.

Kubitza et al.[1] teach administering 5 mg of BAY 59-7939 (rivaroxaban) once daily to male subjects on day 0 and days 4-8 (i.e. five consecutive days) (see page 811a, subjects and methods).

Kubitza et al.[2] teach administering 1.25 mg to 80 mg of BAY 59-7939 (rivaroxaban) under fasting conditions as a tablet to men, wherein BAY 59-7939 showed rapid onset of action (i.e. rapid release as claimed in the instant claims 5, 10, 11, and 14). Kubitza et al. also teach the plasma concentration half life of the tablet containing BAY 59-7939 was observed 2 hours after administration. Kubitza et al. further teach BAY 59-7939 is safe and well-tolerated across a wide range of oral doses (1.25 mg to 80 mg) (see abstract# 3010).

It would have been obvious to one of ordinary skill in the art at the time of the invention to treat deep venous thromboses in a patient by administering rivaroxaban as taught by Straub et al. using the administration guidelines and tablets taught by Kubitza et al.[1] and Kubitza et al.[2] One of ordinary skill in the art would have been motivated to administer rivaroxaban for 5 consecutives days as taught by Kubitza et al.[1] in order to

effectively treat deep vein thromboses. One of ordinary skill in the art would have been motivated to administer rivaroxaban once daily using the rapid release tablet Kubitza et al.[2] in order to provide patient convenience and compliance. One of ordinary skill in the art would have had a reasonable expectation of success in treating deep venous thromboses in a patient by administering rivaroxaban as taught by Straub et al. using the administration guidelines and tablets taught by Kubitza et al.[1] and Kubitza et al.[2] because rivaroxaban is known to treat deep venous thromboses, and Kubitza et al.[1] and Kubitza et al.[2] teach administration guidelines for rivaroxaban that are safe and tolerable for patients.

Conclusion

No claims are allowed.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JODY KAROL whose telephone number is (571)270-3283. The examiner can normally be reached on 8:30 am - 5:00 pm Mon-Fri EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

JLK

/Yong S. Chong/
Primary Examiner, Art Unit 1627

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11883218	MISSELWITZ ET AL.
	Examiner	Art Unit
	JODY KAROL	1627

SEARCHED			
Class	Subclass	Date	Examiner
514	230.8; 236.8 (see attached)	3/9/2011	JLK

SEARCH NOTES		
Search Notes	Date	Examiner
Inventor Search in EAST/PALM	3/9/2011	JLK
EAST Keyword Search (see attached)	3/9/2011	JLK
STIC Search (see attached)	2/17/2011	JLK
STN Search (see attached)	3/9/2011	JLK

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11883218	MISSELWITZ ET AL.
	Examiner	**Art Unit**
	Jody L Karol	1627

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	11/02/2010	03/09/2011							
	1	÷	✓							
	2	÷	✓							
	3	÷	N							
	4	÷	✓							
	5	÷	✓							
	6	÷	✓							
	7	÷	N							
	8	÷	N							
	9		✓							
	10		✓							
	11		✓							
	12		✓							
	13		✓							
	14		✓							

Connecting via Winsock to STN

Welcome to STN International! Enter x:x

LOGINID:SSPTAJLK1617

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * * * * * * Welcome to STN International * * * * * * * * * *

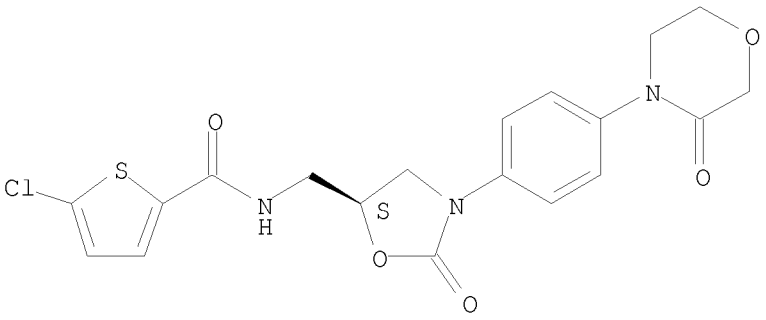
NEWS 1		Web Page for STN Seminar Schedule - N. America
NEWS 2	OCT 04	Precision of EMBASE searching enhanced with new chemical name field
NEWS 3	OCT 06	Increase your retrieval consistency with new formats or for Taiwanese application numbers in CA/CAplus.
NEWS 4	OCT 21	CA/CAplus kind code changes for Chinese patents increase consistency, save time
NEWS 5	OCT 22	New version of STN Viewer preserves custom highlighting of terms when patent documents are saved in .rtf format
NEWS 6	OCT 28	INPADOCDB/INPAFAMDB: Enhancements to the US national patent classification.
NEWS 7	NOV 03	New format for Korean patent application numbers in CA/CAplus increases consistency, saves time.
NEWS 8	NOV 04	Selected STN databases scheduled for removal on December 31, 2010
NEWS 9	NOV 18	PROUSDDR and SYNTHLINE Scheduled for Removal December 31, 2010 by Request of Prous Science
NEWS 10	NOV 22	Higher System Limits Increase the Power of STN Substance-Based Searching
NEWS 11	NOV 24	Search an additional 46,850 records with MEDLINE backfile extension to 1946
NEWS 12	DEC 14	New PNK Field Allows More Precise Crossover among STN Patent Databases
NEWS 13	DEC 18	ReaxysFile available on STN
NEWS 14	DEC 21	CAS Learning Solutions -- a new online training experience
NEWS 15	DEC 22	Value-Added Indexing Improves Access to World Traditional Medicine Patents in CAplus
NEWS 16	JAN 24	The new and enhanced DPCI file on STN has been released
NEWS 17	JAN 26	Improved Timeliness of CAS Indexing Adds Value to USPATFULL and USPAT2 Chemistry Patents
NEWS 18	JAN 26	Updated MeSH vocabulary, new structured abstracts, and other enhancements improve searching in STN reload of MEDLINE
NEWS 19	JAN 28	CABA will be updated weekly
NEWS 20	FEB 23	PCTFULL file on STN completely reloaded
NEWS 21	FEB 23	STN AnaVist Test Projects Now Available for Qualified Customers
NEWS 22	FEB 25	LPCI will be replaced by LDPCI
NEWS 23	MAR 07	Pricing for SELECTing Patent, Application, and Priority Numbers in the USPAT and IFI Database Families is Now Consistent with Similar Patent Databases on STN

NEWS EXPRESS 17 DECEMBER 2010 CURRENT WINDOWS VERSION IS V8.4.2 .1,
AND CURRENT DISCOVER FILE IS DATED 24 JANUARY 2011.

```
 NEWS HOURS    STN Operating Hours Plus Help Desk Availability
 NEWS LOGIN    Welcome Banner and News Items

Enter NEWS followed by the item number or name to see news on that
specific topic.

  All use of STN is subject to the provisions of the STN customer
  agreement.  This agreement limits use to scientific research.  Use
  for software development or design, implementation of commercial
  gateways, or use of CAS and STN data in the building of commercial
  products is prohibited and may result in loss of user privileges
  and other penalties.

* * * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 21:18:22 ON 09 MAR 2011

=> FILE REG
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       0.46       0.46

FILE 'REGISTRY' ENTERED AT 21:19:28 ON 09 MAR 2011
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2011 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:    8 MAR 2011  HIGHEST RN 1266974-31-5
DICTIONARY FILE UPDATES:   8 MAR 2011  HIGHEST RN 1266974-31-5

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH January 14, 2011.

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document.  For information
on property searching in REGISTRY, refer to:

http://www.cas.org/support/stngen/stndoc/properties.html

=> S rivaroxaban/CN
L1            1 RIVAROXABAN/CN

=> D L1

L1   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2011 ACS on STN
RN   366789-02-8  REGISTRY
ED   Entered STN:  05 Nov 2001
CN   2-Thiophenecarboxamide, 5-chloro-N-[[(5S)-2-oxo-3-[4-(3-oxo-4-
     morpholinyl)phenyl]-5-oxazolidinyl]methyl]-  (CA INDEX NAME)
OTHER NAMES:
CN   5-Chloro-N-[[(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-
     yl]methyl]-2-thiophenecarboxamide
CN   5-Chloro-N-[[(S)-3-(4-(3-oxomorpholin-4-yl)phenyl)-2-oxo-1,3-oxazolidin-5-
     yl]methyl]-thiophene-2-carboxamide
```

CN   BAY 59-7939
CN   Rivaroxaban
CN   Xarelto
FS   STEREOSEARCH
DR   931117-62-3, 869880-21-7
MF   C19 H18 Cl N3 O5 S
CI   COM
SR   CAS Client Services
LC   STN Files: ADISINSIGHT, ANABSTR, CA, CAPLUS, CASREACT, CHEMCATS, EMBASE, IMSPATENTS, IMSRESEARCH, IPA, MRCK*, PATDPASPC, PS, TOXCENTER, USAN, USPAT2, USPATFULL
       (*File contains numerically searchable property data)

Absolute stereochemistry. Rotation (-).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

214 REFERENCES IN FILE CA (1907 TO DATE)
3 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
234 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> FILE MEDICINE

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	8.36	8.82

FILE 'ADISCTI' ENTERED AT 21:20:02 ON 09 MAR 2011

FILE 'ADISINSIGHT' ENTERED AT 21:20:02 ON 09 MAR 2011

FILE 'ADISNEWS' ENTERED AT 21:20:02 ON 09 MAR 2011

FILE 'BIOSIS' ENTERED AT 21:20:02 ON 09 MAR 2011

FILE 'BIOTECHNO' ENTERED AT 21:20:02 ON 09 MAR 2011

FILE 'CAPLUS' ENTERED AT 21:20:02 ON 09 MAR 2011

FILE 'DDFB' ENTERED AT 21:20:02 ON 09 MAR 2011
COPYRIGHT (C) 2011 THOMSON REUTERS

FILE 'DDFU' ACCESS NOT AUTHORIZED

FILE 'DGENE' ENTERED AT 21:20:02 ON 09 MAR 2011
COPYRIGHT (C) 2011 THOMSON REUTERS

FILE 'DISSABS' ENTERED AT 21:20:02 ON 09 MAR 2011
COPYRIGHT (C) 2011 ProQuest Information and Learning Company; All Rights Reserved.

FILE 'DRUGB' ENTERED AT 21:20:02 ON 09 MAR 2011
COPYRIGHT (C) 2011 THOMSON REUTERS

FILE 'DRUGU' ENTERED AT 21:20:02 ON 09 MAR 2011
COPYRIGHT (C) 2011 THOMSON REUTERS

FILE 'EMBAL' ENTERED AT 21:20:02 ON 09 MAR 2011
Copyright (c) 2011 Elsevier B.V. All rights reserved.

FILE 'EMBASE' ENTERED AT 21:20:02 ON 09 MAR 2011
Copyright (c) 2011 Elsevier B.V. All rights reserved.

FILE 'ESBIOBASE' ENTERED AT 21:20:02 ON 09 MAR 2011
COPYRIGHT (C) 2011 Elsevier Science B.V., Amsterdam. All rights reserved.

FILE 'IFIPAT' ENTERED AT 21:20:02 ON 09 MAR 2011
COPYRIGHT (C) 2011 IFI CLAIMS(R) Patent Services (IFI)

FILE 'IPA' ENTERED AT 21:20:02 ON 09 MAR 2011
Copyright (c) 2011 The Thomson Corporation

FILE 'KOSMET' ENTERED AT 21:20:02 ON 09 MAR 2011
COPYRIGHT (C) 2011 International Federation of the Societies of Cosmetics Chemists

FILE 'LIFESCI' ENTERED AT 21:20:02 ON 09 MAR 2011
COPYRIGHT (C) 2011 Cambridge Scientific Abstracts (CSA)

FILE 'MEDLINE' ENTERED AT 21:20:02 ON 09 MAR 2011

FILE 'NAPRALERT' ENTERED AT 21:20:02 ON 09 MAR 2011
COPYRIGHT (C) 2011 Board of Trustees of the University of Illinois,
University of Illinois at Chicago.

FILE 'PASCAL' ENTERED AT 21:20:02 ON 09 MAR 2011
Any reproduction or dissemination in part or in full,
by means of any process and on any support whatsoever
is prohibited without the prior written agreement of INIST-CNRS.
COPYRIGHT (C) 2011 INIST-CNRS. All rights reserved.

FILE 'PCTGEN' ENTERED AT 21:20:02 ON 09 MAR 2011
COPYRIGHT (C) 2011 WIPO

FILE 'SCISEARCH' ENTERED AT 21:20:02 ON 09 MAR 2011
Copyright (c) 2011 The Thomson Corporation

FILE 'TOXCENTER' ENTERED AT 21:20:02 ON 09 MAR 2011
COPYRIGHT (C) 2011 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'USGENE' ENTERED AT 21:20:02 ON 09 MAR 2011

```
COPYRIGHT (C) 2011 SEQUENCEBASE CORP

FILE 'USPATFULL' ENTERED AT 21:20:02 ON 09 MAR 2011
CA INDEXING COPYRIGHT (C) 2011 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'USPATOLD' ENTERED AT 21:20:02 ON 09 MAR 2011
CA INDEXING COPYRIGHT (C) 2011 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'USPAT2' ENTERED AT 21:20:02 ON 09 MAR 2011
CA INDEXING COPYRIGHT (C) 2011 AMERICAN CHEMICAL SOCIETY (ACS)

=> S L1
'CN' IS NOT A VALID FIELD CODE
'CN' IS NOT A VALID FIELD CODE
'CN' IS NOT A VALID FIELD CODE
'CN' IS NOT A VALID FIELD CODE
'CN' IS NOT A VALID FIELD CODE
'CN' IS NOT A VALID FIELD CODE
'CN' IS NOT A VALID FIELD CODE
'CN' IS NOT A VALID FIELD CODE
'CN' IS NOT A VALID FIELD CODE
'CN' IS NOT A VALID FIELD CODE
'CN' IS NOT A VALID FIELD CODE
'CN' IS NOT A VALID FIELD CODE
L2        1399 L1

=> L2 and ((deep vein) or (deep venous))
L2 IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> S L2 and ((deep vein) or (deep venous))
L3         424 L2 AND ((DEEP VEIN) OR (DEEP VENOUS))

=> DUP REM L3
DUPLICATE IS NOT AVAILABLE IN 'ADISINSIGHT, ADISNEWS, DGENE, KOSMET, PCTGEN,
USGENE'.
ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE
PROCESSING COMPLETED FOR L3
L4          379 DUP REM L3 (45 DUPLICATES REMOVED)

=> S L4 and pd@<2006
'2006' NOT A VALID FIELD CODE
'2006' NOT A VALID FIELD CODE
'2006' NOT A VALID FIELD CODE
'2006' NOT A VALID FIELD CODE
'2006' NOT A VALID FIELD CODE
'2006' NOT A VALID FIELD CODE
'2006' NOT A VALID FIELD CODE
'2006' NOT A VALID FIELD CODE
'2006' NOT A VALID FIELD CODE
'2006' NOT A VALID FIELD CODE
'2006' NOT A VALID FIELD CODE
'2006' NOT A VALID FIELD CODE
'2006' NOT A VALID FIELD CODE
'2006' NOT A VALID FIELD CODE
'2006' NOT A VALID FIELD CODE
'2006' NOT A VALID FIELD CODE
'2006' NOT A VALID FIELD CODE
'2006' NOT A VALID FIELD CODE
'2006' NOT A VALID FIELD CODE
```

```
'2006' NOT A VALID FIELD CODE
'2006' NOT A VALID FIELD CODE
'2006' NOT A VALID FIELD CODE
'2006' NOT A VALID FIELD CODE
'2006' NOT A VALID FIELD CODE
'2006' NOT A VALID FIELD CODE
'2006' NOT A VALID FIELD CODE
'2006' NOT A VALID FIELD CODE
'2006' NOT A VALID FIELD CODE
L5            0 L4 AND PD@<2006

=> S L4 and @pd<2006
'2006' NOT A VALID FIELD CODE
'2006' NOT A VALID FIELD CODE
'2006' NOT A VALID FIELD CODE
'2006' NOT A VALID FIELD CODE
'2006' NOT A VALID FIELD CODE
'2006' NOT A VALID FIELD CODE
'2006' NOT A VALID FIELD CODE
'2006' NOT A VALID FIELD CODE
'2006' NOT A VALID FIELD CODE
'2006' NOT A VALID FIELD CODE
'2006' NOT A VALID FIELD CODE
'2006' NOT A VALID FIELD CODE
'2006' NOT A VALID FIELD CODE
'2006' NOT A VALID FIELD CODE
'2006' NOT A VALID FIELD CODE
'2006' NOT A VALID FIELD CODE
'2006' NOT A VALID FIELD CODE
'2006' NOT A VALID FIELD CODE
'2006' NOT A VALID FIELD CODE
'2006' NOT A VALID FIELD CODE
'2006' NOT A VALID FIELD CODE
'2006' NOT A VALID FIELD CODE
'2006' NOT A VALID FIELD CODE
'2006' NOT A VALID FIELD CODE
'2006' NOT A VALID FIELD CODE
'2006' NOT A VALID FIELD CODE
'2006' NOT A VALID FIELD CODE
'2006' NOT A VALID FIELD CODE
'2006' NOT A VALID FIELD CODE
L6            0 L4 AND @PD<2006

=> L4 and pd<2006
L4 IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> S L4 and pd<2006
'2006' NOT A VALID FIELD CODE
   8 FILES SEARCHED...
'2006' NOT A VALID FIELD CODE
'2006' NOT A VALID FIELD CODE
'2006' NOT A VALID FIELD CODE
'2006' NOT A VALID FIELD CODE
  21 FILES SEARCHED...
L7           21 L4 AND PD<2006

=> D L7 1-21 IBIB ABS KWIC

L7   ANSWER 1 OF 21  CAPLUS  COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER:        2005:1267623  CAPLUS
```

DOCUMENT NUMBER: 144:266923
TITLE: BAY 59-7939: An oral, direct Factor Xa inhibitor for the prevention of venous thromboembolism in patients after total knee replacement. A phase II dose-ranging study
AUTHOR(S): Turpie, A. G. G.; Fisher, W. D.; Bauer, K. A.; Kwong, L. M.; Irwin, M. W.; Kalebo, P.; Misselwitz, F.; Gent, M.
CORPORATE SOURCE: The ODIXa-Knee Study Group, HHS-General Hospital, Hamilton, Can.
SOURCE: Journal of Thrombosis and Haemostasis (2005), 3(11), 2479-2486
CODEN: JTHOA5; ISSN: 1538-7933
PUBLISHER: Blackwell Publishing, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Background: BAY 59-7939, a novel, oral, direct factor Xa inhibitor, is in clin. development for the prevention of venous thromboembolism (VTE), a frequent complication following orthopaedic surgery. Methods: In a multicenter, parallel-group, double-blind, double-dummy study, 621 patients undergoing elective total knee replacement were randomly assigned to oral BAY 59-7939 (2.5, 5, 10, 20, and 30 mg b.i.d., initiated 6-8 h postsurgery), or s.c. enoxaparin (30 mg b.i.d., initiated 12-24 h postsurgery). Treatment was continued until mandatory bilateral venog. 5-9 days after surgery. The primary efficacy endpoint was a composite of any deep vein thrombosis (proximal and/or distal), confirmed non-fatal pulmonary embolism and all-cause mortality during treatment. The primary safety endpoint was major, postoperative bleeding during treatment. Results: Of the 613 patients treated, 366 (59.7%) were evaluable for the primary efficacy anal. The primary efficacy endpoint occurred in 31.7%, 40.4%, 23.3%, 35.1%, and 25.4% of patients receiving 2.5, 5, 10, 20 and 30 mg b.i.d. doses of BAY 59-7939, resp. (test for trend, P = 0.29), compared with 44.3% in the enoxaparin group. The frequency of major, postoperative bleeding increased with increasing doses of BAY 59-7939 (test for trend, P = 0.0007), with no significant difference between any dose group compared with enoxaparin. Bleeding endpoints were lower for the 2.5-10 mg b.i.d. doses compared with higher doses of BAY 59-7939. Conclusions: Oral administration of 2.5-10 mg b.i.d. of BAY 59-7939, early in the postoperative period, showed potential efficacy and an acceptable safety profile, similar to enoxaparin, for the prevention of VTE in patients undergoing elective total knee replacement.

OS.CITING REF COUNT: 107 THERE ARE 107 CAPLUS RECORDS THAT CITE THIS RECORD (107 CITINGS)
REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

SO Journal of Thrombosis and Haemostasis (2005), 3(11), 2479-2486
CODEN: JTHOA5; ISSN: 1538-7933

AB . . . Treatment was continued until mandatory bilateral venog. 5-9 days after surgery. The primary efficacy endpoint was a composite of any deep vein thrombosis (proximal and/or distal), confirmed non-fatal pulmonary embolism and all-cause mortality during treatment. The primary safety endpoint was major, postoperative. . .

IT 366789-02-8 679809-58-6, Enoxaparin sodium
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(postoperative oral administration of BAY 59-7939 showed potential efficacy, acceptable safety profile similar to enoxaparin for prevention of venous thromboembolism in patient undergoing elective total knee replacement)

L7 ANSWER 2 OF 21 EMBASE

ACCESSION NUMBER: 2007058659 EMBASE
TITLE: Oral anticoagulation - Past, present and future.
AUTHOR: Garipidou, Vassilia, Dr. (correspondence)
CORPORATE SOURCE: Second Propaedeutic Department of Internal Medicine, Aristotle University of Thessaloniki, Greece. gali@med.auth.gr
AUTHOR: Garipidou, Vassilia, Dr. (correspondence)
CORPORATE SOURCE: 9 N. Telloglou str., Thessaloniki 54636, Greece. gali@med.auth.gr
SOURCE: HAEMA, (Nov 2005) Vol. 8, No. SUPPL. 1, pp. S62-S67.
Refs: 25
ISSN: 1108-2682 CODEN: HAGAB8
COUNTRY: Greece
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
025 Hematology
036 Health Policy, Economics and Management
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
ENTRY DATE: Entered STN: 23 Mar 2007
Last Updated on STN: 23 Mar 2007
SO HAEMA, (Nov 2005) Vol. 8, No. SUPPL. 1, pp. S62-S67.
Refs: 25
ISSN: 1108-2682 CODEN: HAGAB8
CT Medical Descriptors:
bleeding: SI, side effect
clinical trial
deep vein thrombosis: DT, drug therapy
drug alcohol interaction
drug bioavailability
drug half life
drug mechanism
drug protein binding
food drug interaction
human
meta analysis
nonhuman
prophylaxis
review
risk assessment
side effect: SI, side. . .
RN. . . acid) 179755-65-8; (acenocoumarol) 152-72-7; (dicoumarol) 66-76-2; (fondaparinux) 104993-28-4, 114870-03-0; (heparin) 37187-54-5, 8057-48-5, 8065-01-8, 9005-48-5; (idraparinux) 149920-56-9, 162610-17-5; (razaxaban) 218298-21-6; (rivaroxaban) 366789-02-8; (warfarin) 129-06-6, 2610-86-8, 3324-63-8, 5543-58-8, 81-81-2; (ximelagatran) 192939-46-1, 260790-58-7

L7 ANSWER 3 OF 21 EMBASE
ACCESSION NUMBER: 2006135137 EMBASE
TITLE: Small molecule coagulation cascade inhibitors in the clinic.
AUTHOR: Saiah, Eddine (correspondence)
CORPORATE SOURCE: Wyeth Research, 200 Cambridge Park Drive, Cambridge, MA 02140, United States. ESaiah@wyeth.com
AUTHOR: Soares, Chris
CORPORATE SOURCE: Amylin Pharmaceuticals, Inc., 9630 Towne Centre Drive, San Diego, CA 92121, United States. Chris.Soares@amylin.com
SOURCE: Current Topics in Medicinal Chemistry, (2005)

Vol. 5, No. 16, pp. 1677-1695.
Refs: 82
ISSN: 1568-0266 CODEN: CTMCCL
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
025 Hematology
036 Health Policy, Economics and Management
037 Drug Literature Index
038 Adverse Reactions Titles
052 Toxicology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 5 Apr 2006
Last Updated on STN: 5 Apr 2006
AB Venous thromboembolic disease, including deep vein thrombosis and pulmonary embolism, is a cause of significant mortality and morbidity. For several decades, anticoagulant options for the treatment and prevention of thrombosis have been limited mainly to agents such as unfractionated heparin and oral vitamin K antagonists such as warfarin. Although these therapies have proven benefits, they also have important limitations that result in their underuse in routine clinical practice. A variety of novel anticoagulants with improved pharmacologic and clinical profiles are in development, offering benefits over traditional therapies. Specifically, progress has been made in the development of small molecule Factor Xa inhibitors and thrombin inhibitors. The most advanced drugs reviewed include DPC-423, DPC-602, razaxaban, GSK's 813893, Portola's Xa inhibitors (formerly Millennium), otamixaban, DU-176b, KFA-1982, BAY-59-7939, DX-9065a, YM-150, LY-517717, Exanta, 3DP's thrombin inhibitors, SSR-182289, LB-30057, LB-30870, BIBR-1048 and Merck's thrombin inhibitors. With their potentially consistent and predictable pharmacological profile, oral formulation, and decreased need for coagulation monitoring, these new agents will likely increase the use and duration of anticoagulation treatment in thromboembolic disorders and reduce the burden associated with long-term management. .COPYRGT. 2005 Bentham Science Publishers Ltd.
SO Current Topics in Medicinal Chemistry, (2005) Vol. 5, No. 16, pp. 1677-1695.
Refs: 82
ISSN: 1568-0266 CODEN: CTMCCL
AB Venous thromboembolic disease, including deep vein thrombosis and pulmonary embolism, is a cause of significant mortality and morbidity. For several decades, anticoagulant options for the treatment. . .
CT Medical Descriptors:
abnormally . . . SI, side effect
alanine aminotransferase blood level
anticoagulation
artery thrombosis: DT, drug therapy
bleeding: SI, side effect
brain hemorrhage: SI, side effect
clinical trial
concentration response
cost effectiveness analysis
deep vein thrombosis: CO, complication
deep vein thrombosis: DT, drug therapy
deep vein thrombosis: PC, prevention
dose response
drug bioavailability
drug blood level
drug competition
drug cost

drug design
drug efficacy
drug metabolism
drug potency
drug potentiation
drug safety
drug selectivity
drug specificity
drug structure
drug synthesis
drug. . .
RN. . . 53663-74-4, 53664-49-6, 63781-77-1; (argatroban) 74863-84-6; (enoxaparin) 9041-08-1; (fondaparinux) 104993-28-4, 114870-03-0; (heparin) 37187-54-5, 8057-48-5, 8065-01-8, 9005-48-5; (otamixaban) 193153-04-7; (razaxaban) 218298-21-6; (rivaroxaban) 366789-02-8; (ximelagatran) 192939-46-1, 260790-58-7

L7 ANSWER 4 OF 21 EMBASE COPYRIGHT (c) 2011 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2005518694 EMBASE
TITLE: Heterogeneity of synthetic factor Xa inhibitors.
AUTHOR: Gerotziafas, Grigoris T.; Samama, Meyer M. (correspondence)
CORPORATE SOURCE: Service d'Hematologie Biologique, Hopital Hotel-Dieu de Paris, 1 Place du Parvis Notre Dame, 75181 Paris Cedex 04, France. mmsamama@aol.com
AUTHOR: Gerotziafas, Grigoris T.
CORPORATE SOURCE: Service of Laboratory Haematology, Attikon University Hospital, Athens, Greece.
AUTHOR: Samama, Meyer M. (correspondence)
CORPORATE SOURCE: Service d'Hematologie Bilogique, Hopital Hotel-Dieu de Paris, 1 Place Parvis Notre Dame, 75181 Paris Cedex 04, France. mmsamama@aol.com
SOURCE: Current Pharmaceutical Design, (2005) Vol. 11, No. 30, pp. 3855-3876.
Refs: 135
ISSN: 1381-6128 CODEN: CPDEFP
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 15 Dec 2005
Last Updated on STN: 15 Dec 2005

AB Heparins and vitamin K antagonists are the landmarks of antithrombotic treatment. Both of them were discovered by serendipity; they are multi-targeted drugs and share several limitations. New molecules have been designed in order to be both more selective concerning their biological target and more homogeneous in their biochemical structure aiming at an improved benefit/risk ratio in the treatment of thrombotic disease. In this article, we will review the pharmacological characteristics of the new synthetic direct or antithrombin dependent inhibitors of FXa in the light of the modern concept of blood coagulation process. We will also present the most recent data from the clinical trials with synthetic inhibitors of FXa. Among them, the synthetic pentasaccharide fondaparinux is the first synthetic and specific FXa inhibitor, which has been approved by health authorities in Europe and in the USA for the prophylaxis of venous thromboembolism in major orthopaedic surgery and is being approved for the treatment of pulmonary embolism and DVT as a single daily subcutaneous injection. The phase II dose-finding

trial of the "meta-pentasaccharide" idraparinux administered subcutaneously once weekly in the secondary prevention of VTE has been completed. DX-9065a is the first direct synthetic inhibitor which has been studied in patients with coronary disease. Razaxaban, BAY59-7939, ZK-807834 and JTV-803 are orally active direct FXa inhibitors, which have been studied in phase II trials. Several other synthetic direct inhibitors of FXa (such as FXV673, YM60828, KFA-1411) are in a preclinical stage of research. From a clinical point of view, the results of recent trials with the synthetic specific FXa inhibitors clearly show that the inhibition of FXa is a critical point in the antithrombotic strategy. .COPYRGT. 2005 Bentham Science Publishers Ltd.

SO Current Pharmaceutical Design, (2005) Vol. 11, No. 30, pp. 3855-3876.
Refs: 135
ISSN: 1381-6128 CODEN: CPDEFP

CT Medical Descriptors:
bleeding: SI, side effect
blood clotting
clinical trial
coronary artery disease: DT, drug therapy
deep vein thrombosis: DT, drug therapy
drug blood level
drug dose regimen
drug half life
drug potentiation
drug structure
drug synthesis
Europe
fibrinolysis
genetic heterogeneity
heparin induced thrombocytopenia: DT, drug therapy
heparin. . .

RN. . . hydroxyphenoxy) 3,5 difluoro 6 [3 (1 methyl 1h 2 imidazolin 2 yl)phenoxy] 4 pyridinyl] n methylglycine) 183305-24-0; (razaxaban) 218298-21-6; (rivaroxaban) 366789-02-8; (warfarin) 129-06-6, 2610-86-8, 3324-63-8, 5543-58-8, 81-81-2

L7 ANSWER 5 OF 21 EMBASE

ACCESSION NUMBER: 2005496954 EMBASE
TITLE: New anticoagulants for venous thromboembolic disease.
AUTHOR: McRae, Simon J., Dr. (correspondence); Ginsberg, Jeffrey S.
CORPORATE SOURCE: Department of Medicine, McMaster University, Hamilton, Ont., Canada. smcrae@mcmaster.ca
AUTHOR: McRae, Simon J., Dr. (correspondence)
CORPORATE SOURCE: McMaster University Medical Centre, HSC 3W11, 1200 Main St West, Hamilton, Ont. L8N 3Z5, Canada. smcrae@mcmaster.ca
SOURCE: Current Opinion in Cardiology, (Nov 2005) Vol. 20, No. 6, pp. 502-508.
Refs: 53
ISSN: 0268-4705 CODEN: COPCE3
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
025 Hematology
036 Health Policy, Economics and Management
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 15 Dec 2005
Last Updated on STN: 15 Dec 2005

AB Purpose of review: In this paper, recent advances in new anticoagulants with the potential to be used for prevention or treatment of venous thrombosis are reviewed. Recent findings: Numerous novel anticoagulants targeting specific stages of the coagulant pathway are in various stages of development. Fondaparinux, an indirect activated factor VII inhibitor, has been shown to be effective for initial treatment and prevention of venous thromboembolism, but still requires parenteral administration. Ximelagatran, an oral direct thrombin inhibitor, has also been shown to effective for treatment and prevention of venous thrombosis. Both agents are associated with bleeding, however, and ximelagatran is associated with hepatic toxicity with long-term use. Direct activated factor X inhibitors, orally available forms of heparin, and other direct thrombin inhibitors remain in early stages of development. Further data on the clinical utility of these agents are likely to emerge in the next few years, and uptake of their use will be affected by the cost considerations. Summary: Numerous alternative anticoagulants are in varying stages of development. Clinical data have yet to show that these agents have a clearly superior risk-benefit ratio compared with currently used antithrombotics. Many drugs remain in initial stages of development. The ideal anticoagulant agent is being sought but has yet to be discovered. .COPYRGT. 2005 Lippincott Williams & Wilkins.

SO Current Opinion in Cardiology, (Nov 2005) Vol. 20, No. 6, pp. 502-508.
Refs: 53
ISSN: 0268-4705 CODEN: COPCE3

CT Medical Descriptors:
abnormally high substrate concentration in blood: SI, side effect
alanine aminotransferase blood level
bleeding: SI, side effect
clinical trial
*deep vein thrombosis: DM, disease management
*deep vein thrombosis: DT, drug therapy
drug absorption
drug cost
drug effect
drug efficacy
hepatorenal syndrome: SI, side effect
human
liver failure: SI, side effect
liver toxicity: SI, side. . .

RN. . . (enoxaparin) 9041-08-1; (fondaparinux) 104993-28-4, 114870-03-0; (heparin) 37187-54-5, 8057-48-5, 8065-01-8, 9005-48-5; (hirudin) 8001-27-2; (lepirudin) 138068-37-8; (melagatran) 159776-70-2; (recombinant thrombomodulin) 120313-91-9; (rivaroxaban) 366789-02-8; (warfarin) 129-06-6, 2610-86-8, 3324-63-8, 5543-58-8, 81-81-2; (ximelagatran) 192939-46-1, 260790-58-7

L7 ANSWER 6 OF 21 EMBASE

ACCESSION NUMBER: 2005418141 EMBASE
TITLE: Long-term anticoagulation: The prospects for alternatives to warfarin.
AUTHOR: Ansell, Jack, Dr. (correspondence)
CORPORATE SOURCE: Department of Medicine, Boston University Medical Center, 88 East Newton Street, Boston, MA 02118, United States. jack.Ansell@bmc.org
SOURCE: Seminars in Vascular Surgery, (Sep 2005) Vol. 18, No. 3 SPEC. ISS., pp. 134-138.
Refs: 22
ISSN: 0895-7967 CODEN: SVSUEP
PUBLISHER IDENT.: S 0895-7967(05)00024-4
COUNTRY: United States

DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
030 Clinical and Experimental Pharmacology
036 Health Policy, Economics and Management
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 13 Oct 2005
Last Updated on STN: 13 Oct 2005

AB Many advances have occurred in the pharmacological treatment of venous thromboembolism (VTE) since the vitamin K antagonists (eg, warfarin) and unfractionated heparin were introduced over 60 years ago, but warfarin and other coumarin derivatives remain the only orally administered anticoagulants available for long-term prevention and treatment of VTE. The coumarin derivatives are not convenient to use, as they have a narrow therapeutic index and require frequent laboratory monitoring and dosage adjustment. The low-molecular-weight heparins, and the indirect factor Xa inhibitor, fondaparinux, offer improvements, but both agents still need to be administered subcutaneously. A number of new, orally available, direct inhibitors of factor Xa or thrombin are in development and offer ease of use and predictability of dosing so that monitoring is not required. These agents hold great promise as new anticoagulants that might provide greater efficacy and safety, and because of these attributes, might lead to greater use of anticoagulant therapy for patients not currently treated. .COPYRGT. 2005 Elsevier Inc. All rights reserved.

SO Seminars in Vascular Surgery, (Sep 2005) Vol. 18, No. 3 SPEC. ISS., pp. 134-138.
Refs: 22
ISSN: 0895-7967 CODEN: SVSUEP

CT Medical Descriptors:
abnormally high substrate concentration in blood: SI, side effect
age distribution
alanine aminotransferase blood level
*anticoagulant therapy
article
bleeding: SI, side effect
brain hemorrhage: SI, side effect
clinical trial
deep vein thrombosis: DT, drug therapy
drug blood level
drug excretion
drug half life
drug metabolism
drug monitoring
drug safety
food drug interaction
heparin induced thrombocytopenia: DT, drug therapy
heparin. . .

RN. . . (fondaparinux) 104993-28-4, 114870-03-0; (heparin) 37187-54-5, 8057-48-5, 8065-01-8, 9005-48-5; (hirulog) 128270-60-0; (idraparinux) 149920-56-9, 162610-17-5; (lepirudin) 138068-37-8; (melagatran) 159776-70-2; (razaxaban) 218298-21-6; (rivaroxaban) 366789-02-8; (warfarin) 129-06-6, 2610-86-8, 3324-63-8, 5543-58-8, 81-81-2; (ximelagatran) 192939-46-1, 260790-58-7

L7 ANSWER 7 OF 21 EMBASE COPYRIGHT (c) 2011 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2005357852 EMBASE
TITLE: New antithrombotics in the prevention of thromboembolic disease.
AUTHOR: Yavin, Yshai Y.; Wolozinsky, Mia; Cohen, Alexander T.

(correspondence)
CORPORATE SOURCE: Vascular Medicine, Department of Surgery, Guy's, King's and St. Thomas School of Medicine, London SE5 9PJ, United Kingdom. alexander.cohen@kcl.ac.uk
SOURCE: European Journal of Internal Medicine, (Aug 2005) Vol. 16, No. 4, pp. 257-266.
Refs: 44
ISSN: 0953-6205 CODEN: EJIMEJ
PUBLISHER IDENT.: S 0953-6205(05)00123-8
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Conference Article; (Conference paper)
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
037 Drug Literature Index
038 Adverse Reactions Titles
006 Internal Medicine
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 9 Sep 2005
Last Updated on STN: 9 Sep 2005
AB New anticoagulants are under development to improve on current ones that, although effective, have limitations in efficacy, safety and convenience. We have reviewed the use of these agents as thromboprophylactic drugs. These new agents have more specific modes of action and can be divided into three groups. Inhibitors of the initiation of coagulation work via inhibition of the factor VIIa/tissue factor complex. Inhibitors of propagation of coagulation include parenteral and oral factor Xa inhibitors, factor IXa inhibitors, inhibitors of factor Va and VIIIa, activated Protein C, soluble thrombomodulin and SNAC-Heparin. Finally, direct inhibitors of thrombin are under development both for parenteral and oral administration. Several new drugs, such as fondaparinux, hirudin, argatroban, bivalirudin and ximelagatran, have already been licensed for specific indications and are being investigated for more general usage. Other drugs reviewed are in much earlier stages of development. .COPYRGT. 2005 European Federation of Internal Medicine. Published by Elsevier B.V. All rights reserved.
SO European Journal of Internal Medicine, (Aug 2005) Vol. 16, No. 4, pp. 257-266.
Refs: 44
ISSN: 0953-6205 CODEN: EJIMEJ
CT Medical Descriptors:
bleeding: SI, side effect
blood clotting
clinical trial
conference paper
deep vein thrombosis: DT, drug therapy
deep vein thrombosis: PC, prevention
drug efficacy
drug safety
fibrin formation
human
lung embolism: DT, drug therapy
lung embolism: PC, prevention
postoperative complication: CO, complication
postoperative complication: DT, drug. . .
RN. . . (fondaparinux) 104993-28-4, 114870-03-0; (heparin) 37187-54-5, 8057-48-5, 8065-01-8, 9005-48-5; (hirudin) 8001-27-2; (hirulog) 128270-60-0; (idraparinux) 149920-56-9, 162610-17-5; (melagatran) 159776-70-2; (razaxaban) 218298-21-6; (rivaroxaban) 366789-02-8; (thrombomodulin) 112049-68-0; (tissue factor pathway inhibitor) 116638-34-7; (warfarin) 129-06-6, 2610-86-8, 3324-63-8, 5543-58-8, 81-81-2; (ximelagatran) 192939-46-1, 260790-58-7

L7 ANSWER 8 OF 21 EMBASE COPYRIGHT (c) 2011 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2005303226 EMBASE
TITLE: Annual update 2004/2005 - Treatment of cardiovascular disorders.
AUTHOR: Prous, J.R.
SOURCE: Drugs of the Future, (Apr 2005) Vol. 30, No. 4, pp. 369-376.
ISSN: 0377-8282 CODEN: DRFUD4
COUNTRY: Spain
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
006 Internal Medicine
LANGUAGE: English
ENTRY DATE: Entered STN: 28 Jul 2005
Last Updated on STN: 28 Jul 2005
SO Drugs of the Future, (Apr 2005) Vol. 30, No. 4, pp. 369-376.
ISSN: 0377-8282 CODEN: DRFUD4
CT Medical Descriptors:
*angina . . . therapy
coronary artery bypass graft
*coronary artery disease: DI, diagnosis
*coronary artery disease: DT, drug therapy
*coronary artery disease: SU, surgery
*coronary artery disease: TH, therapy
deep vein thrombosis: DT, drug therapy
deep vein thrombosis: PC, prevention
drug indication
drug research
gene therapy
graft failure: CO, complication
graft failure: DT, drug therapy
*heart arrhythmia: DT, drug therapy
heart atrium fibrillation:. . .
RN. . . 2465-59-0; (paclitaxel) 33069-62-4; (pactimibe) 189198-30-9; (pexelizumab) 219685-93-5; (prasugrel) 389574-19-0; (probucol succinate) 216167-82-7; (ranolazine) 95635-55-5; (recombinant thrombomodulin) 120313-91-9; (regadenoson) 313348-27-5; (rivaroxaban) 366789-02-8 ; (sarpogrelate) 125926-17-2, 135159-51-2, 86819-20-7; (staphylokinase) 9040-61-3; (tecadenoson) 204512-90-3; (tedisamil) 90961-53-8; (tolvaptan) 150683-30-0; (torcetrapib) 262352-17-0; (trientine) 112-24-3, 38260-01-4; (uniprost) 81846-19-7; (valsartan). . .

L7 ANSWER 9 OF 21 EMBASE COPYRIGHT (c) 2011 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2005251437 EMBASE
TITLE: Optimizing antiplatelet and anticoagulant agents in the perioperative orthopedic surgery patient.
AUTHOR: Oh, Jennifer J. (correspondence); Akers, Wendell S.
CORPORATE SOURCE: University of Kentucky, College of Pharmacy, 725 Rose St., Lexington, KY 40536, United States.
AUTHOR: Robon, Matthew J.
CORPORATE SOURCE: Department of Orthopedic Surgery, Medical College of Ohio, Toledo, OH, United States.
SOURCE: Orthopedics, (May 2005) Vol. 28, No. 5, pp. 453-458.
Refs: 17
ISSN: 0147-7447 CODEN: ORTHDK
COUNTRY: United States
DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 025 Hematology
030 Clinical and Experimental Pharmacology
033 Orthopedic Surgery
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 23 Jun 2005
Last Updated on STN: 23 Jun 2005
AB This month's Pharmacology Update addresses advantages, disadvantages and updated recommendations on anticoagulant agents.
SO Orthopedics, (May 2005) Vol. 28, No. 5, pp. 453-458.
Refs: 17
ISSN: 0147-7447 CODEN: ORTHDK
CT Medical Descriptors:
*anticoagulation
article
bleeding: DT, drug therapy
bleeding: SI, side effect
bleeding tendency: SI, side effect
cardiovascular disease: CO, complication
cardiovascular disease: DT, drug therapy
cardiovascular disease: PC, prevention
clinical trial
deep vein thrombosis: CO, complication
deep vein thrombosis: DT, drug therapy
deep vein thrombosis: PC, prevention
digestive system ulcer: SI, side effect
drug absorption
drug bioavailability
drug blood level
drug elimination
drug half life
drug mechanism
drug metabolism
drug penetration
drug research
gastritis:. . .
RN. . . 9005-48-5; (hirulog) 128270-60-0; (idraparinux) 149920-56-9, 162610-17-5; (lepirudin) 138068-37-8; (omeprazole) 73590-58-6, 95510-70-6; (piroxicam) 36322-90-4; (protamine) 11061-43-1, 9007-31-2, 9012-00-4; (razaxaban) 218298-21-6; (rivaroxaban) 366789-02-8; (ticlopidine) 53885-35-1, 55142-85-3; (warfarin) 129-06-6, 2610-86-8, 3324-63-8, 5543-58-8, 81-81-2

L7 ANSWER 10 OF 21 EMBASE
ACCESSION NUMBER: 2005198128 EMBASE
TITLE: New anticoagulants: Beyond heparin, low-molecular-weight heparin and warfarin.
AUTHOR: Bates, Shannon M.; Weitz, Jeffrey I. (correspondence)
CORPORATE SOURCE: Department of Medicine, McMaster University, Henderson Research Centre, Hamilton, Ont., Canada. jweitz@thrombosis.hhscr.org
AUTHOR: Weitz, Jeffrey I. (correspondence)
CORPORATE SOURCE: Department of Biochemistry, McMaster University, Hamilton, Ont., Canada. jweitz@thrombosis.hhscr.org
AUTHOR: Weitz, Jeffrey I. (correspondence)
CORPORATE SOURCE: Henderson Research Centre, 711 Concession Street, Hamilton, Ont. L8V 1C3, Canada. jweitz@thrombosis.hhscr.org
SOURCE: British Journal of Pharmacology, (Apr 2005) Vol. 144, No. 8, pp. 1017-1028.

Refs: 135
ISSN: 0007-1188 CODEN: BJPCBM
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 030 Clinical and Experimental Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 26 May 2005
Last Updated on STN: 26 May 2005
AB The limitations of traditional anticoagulants, heparin and warfarin, have prompted the development of new anticoagulant drugs for prevention and treatment of both venous and arterial thromboembolism. After a brief review of thrombogenesis and its regulation, this paper focuses on new anticoagulant agents in more advanced stages of clinical testing.

SO British Journal of Pharmacology, (Apr 2005) Vol. 144, No. 8, pp. 1017-1028.
Refs: 135
ISSN: 0007-1188 CODEN: BJPCBM
CT Medical Descriptors:
artery thrombosis: DT, drug therapy
artery thrombosis: PC, prevention
bleeding: SI, side effect
brain hemorrhage: SI, side effect
clinical trial
deep vein thrombosis: DT, drug therapy
deep vein thrombosis: PC, prevention
drug efficacy
drug safety
heart atrium fibrillation: DT, drug therapy
heart muscle ischemia: DT, drug therapy
heparin induced thrombocytopenia: DT, drug. . .
RN. . . 8065-01-8, 9005-48-5; (hirudin) 8001-27-2; (hirulog) 128270-60-0; (idraparinux) 149920-56-9, 162610-17-5; (melagatran) 159776-70-2; (protamine sulfate) 9009-65-8; (razaxaban) 218298-21-6; (recombinant thrombomodulin) 120313-91-9; (rivaroxaban) 366789-02-8; (warfarin) 129-06-6, 2610-86-8, 3324-63-8, 5543-58-8, 81-81-2; (ximelagatran) 192939-46-1, 260790-58-7

L7 ANSWER 11 OF 21 EMBASE
ACCESSION NUMBER: 2005179532 EMBASE
TITLE: Treatment of venous thromboembolism.
AUTHOR: Eichinger, Sabine, Dr. (correspondence)
CORPORATE SOURCE: Department of Internal Medicine I, Medical University of Vienna, Wahringer Gurtel 18-20, 1090 Vienna, Austria. sabine.eichinger@meduniwien.ac.at
SOURCE: Wiener Medizinische Wochenschrift, (Jan 2005) Vol. 155, No. 1-2, pp. 7-10.
Refs: 11
ISSN: 0043-5341 CODEN: WMWOA4
COUNTRY: Austria
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English; German
ENTRY DATE: Entered STN: 5 May 2005
Last Updated on STN: 5 May 2005
AB Deep vein thrombosis (DVT) and pulmonary embolism (PE)

are two manifestations of the same disorder, venous thromboembolism, and low-molecular weight heparin is the treatment of choice for both DVT and PE. Alternatively, intravenous adjusted-dose unfractionated heparin can be used in hemodynamically unstable patients with massive PE. Secondary thromboprophylaxis with vitamin K-antagonists (VKA) should be started as soon as the diagnosis is confirmed. The dose of VKA should be adjusted to a target international normalized ratio (INR) of 2.5. For most patients with PE, thrombolysis is not recommended. Vena cava filters should be restricted to patients with active bleeding or risk of serious bleeding, and to those in whom PE has recurred despite adequate anticoagulation. Several new antithrombotics with potential advantages over heparin and VKA have been evaluated in phase II and III trials, but are currently not licensed for the treatment of venous thromboembolic events. .COPYRGT. Springer-Verlag 2005.

SO Wiener Medizinische Wochenschrift, (Jan 2005) Vol. 155, No. 1-2, pp. 7-10.
Refs: 11
ISSN: 0043-5341 CODEN: WMWOA4

AB Deep vein thrombosis (DVT) and pulmonary embolism (PE) are two manifestations of the same disorder, venous thromboembolism, and low-molecular weight heparin is. . .

CT Medical Descriptors:
anticoagulant therapy
article
bleeding
blood clot lysis
clinical trial
*deep vein thrombosis: DT, drug therapy
human
international normalized ratio
*lung embolism: DT, drug therapy
partial thromboplastin time
prophylaxis
secondary prevention
thrombosis prevention
vena cava filter
*venous thromboembolism: DT, drug. . .

RN (enoxaparin) 9041-08-1; (fondaparinux) 104993-28-4, 114870-03-0; (heparin) 37187-54-5, 8057-48-5, 8065-01-8, 9005-48-5; (idraparinux) 149920-56-9, 162610-17-5; (razaxaban) 218298-21-6; (rivaroxaban) 366789-02-8; (ximelagatran) 192939-46-1, 260790-58-7

L7 ANSWER 12 OF 21 EMBASE COPYRIGHT (c) 2011 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2005099623 EMBASE
TITLE: New anticoagulant therapy.
AUTHOR: Linkins, Lori-Ann (correspondence); Weitz, Jeffrey I.
CORPORATE SOURCE: McMaster Univ./Henderson Res. Ctr., Hamilton, Ont. L8V 1C3, Canada. jweitz@thrombosis.hhscr.org; llinkins@thrombosis.hhscr.org
SOURCE: Annual Review of Medicine, (2005) Vol. 56, pp. 63-77.
Refs: 47
ISSN: 0066-4219 CODEN: ARMCAH
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 24 Mar 2005

Last Updated on STN: 6 Sep 2007

AB The development of new anticoagulants is expanding the list of drugs that can be used to prevent and treat venous and arterial thrombosis. New parenteral anticoagulants have been developed to overcome the limitations of heparin and low-molecular-weight heparin, whereas novel orally active anticoagulants have been designed to provide more streamlined therapy than vitamin K antagonists. This review identifies the molecular targets of new anticoagulants, describes the results of clinical trials, and provides clinical perspective on the opportunities for new anticoagulants.

SO Annual Review of Medicine, (2005) Vol. 56, pp. 63-77.
Refs: 47
ISSN: 0066-4219 CODEN: ARMCAH

CT Medical Descriptors:
adult
aged
*anticoagulation
artery thrombosis: DT, drug therapy
bleeding: SI, side effect
clinical trial
controlled study
deep vein thrombosis: DT, drug therapy
heart atrium fibrillation: DT, drug therapy
heart muscle ischemia: DT, drug therapy
human
liver dysfunction: SI, side effect
major clinical. . .

RN. . . (fondaparinux) 104993-28-4, 114870-03-0; (heparin) 37187-54-5, 8057-48-5, 8065-01-8, 9005-48-5; (hirudin) 8001-27-2; (hirulog) 128270-60-0; (idraparinux) 149920-56-9, 162610-17-5; (melagatran) 159776-70-2; (razaxaban) 218298-21-6; (rivaroxaban) 366789-02-8; (thrombomodulin) 112049-68-0; (warfarin) 129-06-6, 2610-86-8, 3324-63-8, 5543-58-8, 81-81-2; (ximelagatran) 192939-46-1, 260790-58-7

L7 ANSWER 13 OF 21 EMBASE

ACCESSION NUMBER: 2005097260 EMBASE
TITLE: Emerging strategies for treatment of venous thromboembolism.
AUTHOR: Prandoni, Paolo, Prof. (correspondence)
CORPORATE SOURCE: University of Padua, Dept. of Med. and Surgical Sciences, 2nd Chair of Internal Medicine, Via Ospedale Civile 105, 35128, Padua, Italy. paoloprandoni@tin.ir
SOURCE: Expert Opinion on Emerging Drugs, (Feb 2005) Vol. 10, No. 1, pp. 87-94.
Refs: 46
ISSN: 1472-8214 CODEN: EOEDA3
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
030 Clinical and Experimental Pharmacology
036 Health Policy, Economics and Management
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 24 Mar 2005
Last Updated on STN: 24 Mar 2005

AB Although considerable progress has been made in the treatment of venous thromboembolism (VTE), many unanswered questions remain, which are awaiting proper solution. Furthermore, new opportunities are emerging, which have the potential to rapidly change the therapeutic scenario.

Selected patients with deep-vein thrombosis can be effectively and safely treated at home with fixed-dose low-molecular-weight heparins. The long-term use of low-molecular-weight heparins is likely to be more effective than and as safe as oral anticoagulants for the secondary prevention of VTE in cancer patients with venous thrombosis. Recent publications have unexpectedly raised a renewed interest on the use of thrombolytic drugs in patients with pulmonary embolism, at least in those who present with heart ventricular dysfunction. The optimal long-term treatment of VTE is still undefined. Finally, new categories of drugs are emerging, which have the potential to replace conventional anticoagulants in the near future. They include anti-Xa inhibitors, such as pentasaccharide, and antithrombin inhibitors, such as ximelagatran.

SO Expert Opinion on Emerging Drugs, (Feb 2005) Vol. 10, No. 1, pp. 87-94.
Refs: 46
ISSN: 1472-8214 CODEN: EOEDA3

AB . . . proper solution. Furthermore, new opportunities are emerging, which have the potential to rapidly change the therapeutic scenario. Selected patients with deep-vein thrombosis can be effectively and safely treated at home with fixed-dose low-molecular-weight heparins. The long-term use of low-molecular-weight heparins is. . .

RN. . . 114870-03-0; (heparin) 37187-54-5, 8057-48-5, 8065-01-8, 9005-48-5; (hirudin) 8001-27-2; (hirulog) 128270-60-0; (idraparinux) 149920-56-9, 162610-17-5; (melagatran) 159776-70-2; (nadroparin) 104521-37-1; (razaxaban) 218298-21-6; (rivaroxaban) 366789-02-8; (warfarin) 129-06-6, 2610-86-8, 3324-63-8, 5543-58-8, 81-81-2; (ximelagatran) 192939-46-1, 260790-58-7

L7 ANSWER 14 OF 21 EMBASE COPYRIGHT (c) 2011 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2004455722 EMBASE
TITLE: The direct thrombin inhibitor melagatran/ximelagatran.
AUTHOR: Brighton, Timothy A., Dr. (correspondence)
CORPORATE SOURCE: Department of Haematology, St. George Hospital, Gray Street, Kogarah, NSW 2217, Australia. t.brighton@unsw.edu.au
AUTHOR: Brighton, Timothy A., Dr. (correspondence)
CORPORATE SOURCE: St. George Clinical School, University of New South Wales, Sydney, NSW, Australia. t.brighton@unsw.edu.au
SOURCE: Medical Journal of Australia, (18 Oct 2004) Vol. 181, No. 8, pp. 432-437.
Refs: 24
ISSN: 0025-729X CODEN: MJAUAJ
COUNTRY: Australia
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
025 Hematology
036 Health Policy, Economics and Management
037 Drug Literature Index
038 Adverse Reactions Titles
006 Internal Medicine
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 12 Nov 2004
Last Updated on STN: 12 Nov 2004

AB • Melagatran is a synthetic, small-peptide direct thrombin inhibitor with anticoagulant activity. • Ximelagatran, an oral prodrug, undergoes rapid enzymatic conversion to melagatran. • Melagatran has rapid onset of action, fixed twice-daily dosing, stable absorption, apparent low potential for medication interactions, and no requirement for

monitoring drug levels or dose adjustment. There is no specific antidote, but the drug has a short plasma elimination half-life (about 4 hours). • In clinical studies, melagatran/ximelagatran is not inferior to warfarin for stroke prevention in patients with non-valvular atrial fibrillation, to heparin-warfarin for acute treatment and extended secondary prevention of deep vein thrombosis, and superior to warfarin for prevention of venous thromboembolism after major orthopaedic surgery. Major bleeding with melagatran/ximelagatran occurred at rates similar to those in patients treated with warfarin. • 6%-12% of patients taking ximelagatran develop asymptomatic elevated liver enzyme levels (predominantly alanine aminotransferase) after 1-6 months of therapy; this usually resolves with cessation of therapy. Less than 1% of patients develop abnormal liver function while taking ximelagatran; this rarely persists or develops into clinical illness.

SO Medical Journal of Australia, (18 Oct 2004) Vol. 181, No. 8, pp. 432-437.
Refs: 24
ISSN: 0025-729X CODEN: MJAUAJ

AB . . . warfarin for stroke prevention in patients with non-valvular atrial fibrillation, to heparin-warfarin for acute treatment and extended secondary prevention of deep vein thrombosis, and superior to warfarin for prevention of venous thromboembolism after major orthopaedic surgery. Major bleeding with melagatran/ximelagatran occurred atomic . .

CT Medical Descriptors:
*anticoagulant therapy
anticoagulation
article
bleeding: SI, side effect
clinical trial
deep vein thrombosis: DM, disease management
deep vein thrombosis: DT, drug therapy
deep vein thrombosis: PC, prevention
dose calculation
dose kidney function relation
dose time effect relation
drug absorption
drug alcohol interaction
drug bioavailability
drug blood level
drug cost
drug efficacy
drug elimination
drug. . .

RN. . . (fondaparinux) 104993-28-4, 114870-03-0; (heparin) 37187-54-5, 8057-48-5, 8065-01-8, 9005-48-5; (hirudin) 8001-27-2; (idraparinux) 149920-56-9, 162610-17-5; (melagatran) 159776-70-2; (nifedipine) 21829-25-4; (razaxaban) 218298-21-6; (rivaroxaban) 366789-02-8; (vitamin K group) 12001-79-5; (warfarin) 129-06-6, 2610-86-8, 3324-63-8, 5543-58-8, 81-81-2; (ximelagatran) 192939-46-1, 260790-58-7

L7 ANSWER 15 OF 21 EMBASE

ACCESSION NUMBER: 2003182018 EMBASE
TITLE: Factor Xa inhibitors: Today and beyond.
AUTHOR: Walenga, Jeanine M. (correspondence); Jeske, Walter P.; Hoppensteadt, Debra; Fareed, Jawed
CORPORATE SOURCE: Department of Pathology, Loyola University, Medical Center, 2160 S First Avenue, Maywood, IL 60153, United States. jwaleng@lumc.edu
AUTHOR: Walenga, Jeanine M. (correspondence); Jeske, Walter P.
CORPORATE SOURCE: Dept. of Thoracic-Cardivasc. Surg., Loyola University,

Medical Center, 2160 S First Avenue, Maywood, IL 60153, United States. jwaleng@lumc.edu
SOURCE: Current Opinion in Investigational Drugs, (1 Mar 2003) Vol. 4, No. 3, pp. 272-281.
Refs: 120
ISSN: 1472-4472 CODEN: CIDREE
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
025 Hematology
030 Clinical and Experimental Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 22 May 2003
Last Updated on STN: 22 May 2003

AB Serine proteases play an important role in thrombogenesis, the process that leads to blood clotting and conditions such as heart attack, stroke and other cardiovascular disorders. In the coagulation network, the activation of various serine proteases facilitates the formation of the serine protease Factor Xa, which plays a central role in the process of coagulation and platelet activation. Factor Xa is an essential component of the prothrombinase complex, from which thrombin is formed, which then directly leads to fibrin clot formation. Thus, the inhibition of Factor Xa and its generation is an important strategy in the development of new antithrombotic drugs.

SO Current Opinion in Investigational Drugs, (1 Mar 2003) Vol. 4, No. 3, pp. 272-281.
Refs: 120
ISSN: 1472-4472 CODEN: CIDREE

CT Medical Descriptors:
atherosclerosis: DT, drug therapy
bleeding: SI, side effect
blood clotting
cardiovascular disease: DT, drug therapy
clinical trial
deep vein thrombosis: DT, drug therapy
dose response
drug bioavailability
drug efficacy
drug elimination
drug half life
drug mechanism
drug monitoring
drug potency
drug safety
enzyme activation
fibrin clot
heart infarction: DT, drug. . .

RN. . . amidino 2 hydroxyphenoxy) 3,5 difluoro 6 [3 (1 methyl 1h 2 imidazolin 2 yl)phenoxy] 4 pyridinyl] n methylglycine) 183305-24-0; (rivaroxaban) 366789-02-8; (serine proteinase) 37259-58-8; (thrombin) 9002-04-4

L7 ANSWER 16 OF 21 IPA COPYRIGHT (c) 2011 The Thomson Corporation on STN

ACCESSION NUMBER: 2010:10477 IPA
DOCUMENT NUMBER: 47-12238
TITLE: Rivaroxaban for Thromboprophylaxis in Patients Undergoing Major Orthopedic Surgery
AUTHOR: Melillo, SN; Scanlon, JV; Exter, BP; Steinberg, M; Jarvis,

CI
CORPORATE SOURCE: Massachusetts Coll Pharm & Hlth Sci, Sch Pharm, 19 Foster St, Worcester, MA 01608, USA stephanie.melillo@mcphs.edu
SOURCE: European Journal of Dermatology (France), (2002) Vol. 12, pp. 1061-1071. 55 Refs.
CODEN: EJDEE; ISSN: 1167-1122.
DOCUMENT TYPE: Journal
FILE SEGMENT: HUMAN
LANGUAGE: English
AB OBJECTIVE: To review the pharmacology, pharmacokinetics, and clinical efficacy/safety profile of rivaroxaban to inform health-care professionals of this new agent for the prevention of venous thromboembolism (VTE) in patients undergoing major orthopedic surgery.

DATA SOURCES: A literature search was performed in PubMed/MEDLINE (1966 March 2010), International Pharmaceutical Abstracts (1970 March 2010), and EMBASE (1990 March 2010), limited to publications in English, using the search terms BAY 59-7939, rivaroxaban, factor Xa inhibitor, hip replacement, and/or knee replacement to identify literature sources. References from retrieved articles were evaluated to identify relevant literature. Unpublished Phase 3 clinical trials in progress (using www.clinicaltrials.gov) were also reviewed. The Food and Drug Administration, European Medicines Agency, and Health Canada Web sites were used to retrieve product monographs, regulatory guidance, and advisory committee briefing packets.

STUDY SELECTION AND DATA EXTRACTION: All available studies relevant to the pharmacology, pharmacokinetics, and clinical safety/efficacy of rivaroxaban for the prevention of VTE in patients undergoing major orthopedic surgery were included, with preference for clinical data.

DATA SYNTHESIS: Rivaroxaban use was significantly more effective for thrombo-prophylaxis in patients undergoing total knee replacement (TKR) or total hip replacement (THR), compared to enoxaparin for the composite incidence of deep vein thrombosis, nonfatal pulmonary embolism, all-cause mortality, and the rate of major VTE; bleeding events occurred at statistically similar rates. In Phase 3 studies, rivaroxaban 10 mg was administered orally 6-8 hours post-surgery and post-hemostasis. Thereafter, administration was once daily for 35 days in THR and 10-14 days in TKR.

CONCLUSIONS: Rivaroxaban has demonstrated comparable safety and superior efficacy to the commonly used low-molecular-weight heparin, enoxaparin. Ongoing and future clinical trials will allow clinicians to further assess the efficacy, safety, and pharmacoeconomics of rivaroxaban.
SO European Journal of Dermatology (France), (2002) Vol. 12, pp. 1061-1071. 55 Refs.
CODEN: EJDEE; ISSN: 1167-1122.
AB . . . in patients undergoing total knee replacement (TKR) or total hip replacement (THR), compared to enoxaparin for the composite incidence of deep vein thrombosis, nonfatal pulmonary embolism, all-cause mortality, and the rate of major VTE; bleeding events occurred at statistically similar rates. In. . .
RN 366789-02-8 (Rivaroxaban)

L7 ANSWER 17 OF 21 USPATFULL on STN
ACCESSION NUMBER: 2005:209571 USPATFULL
TITLE: Preparation process
INVENTOR(S): Berwe, Mathias, Sprockhovel, GERMANY, FEDERAL REPUBLIC OF
Thomas, Christian, Wuppertal, GERMANY, FEDERAL REPUBLIC OF
Rehse, Joachim, Leichlingen, GERMANY, FEDERAL REPUBLIC OF
Grotjohann, Dirk, Leverkusen, GERMANY, FEDERAL REPUBLIC OF

PATENT ASSIGNEE(S): Bayer HealthCare AG, Leverkusen, GERMANY, FEDERAL REPUBLIC OF, 51368 (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 20050182055	A1	20050818	<--
	US 7351823	B2	20080401	
APPLICATION INFO.:	US 2005-32815	A1	20050110	(11)

	NUMBER	DATE
PRIORITY INFORMATION:	DE 2004-10200	20040115

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: JEFFREY M. GREENMAN, BAYER PHARMACEUTICALS CORPORATION, 400 MORGAN LANE, WEST HAVEN, CT, 06516, US
NUMBER OF CLAIMS: 16
EXEMPLARY CLAIM: 1
LINE COUNT: 357
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to a process for preparing 5-chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide starting from 2-[(2S)-2-oxiranylmethyl]-1H-isoindole-1,3(2H)-dione, 4-(4-aminophenyl)-3-morpholinone and 5-chlorothiophene-2-carbonyl chloride.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . angina), reocclusions and restenoses after angioplasty or aortocoronary bypass, stroke, transient ischaemic attacks, peripheral arterial occlusive diseases, pulmonary embolisms or deep venous thromboses.
IT 366789-02-8P
(preparation of rivaroxaban)

L7 ANSWER 18 OF 21 USPATFULL on STN
ACCESSION NUMBER: 2004:307984 USPATFULL
TITLE: Substituted oxazolidinones for combinational therapy
INVENTOR(S): Straub, Alexander, Wuppertal, GERMANY, FEDERAL REPUBLIC OF
Lampe, Thomas, Dusseldorf, GERMANY, FEDERAL REPUBLIC OF
Pernerstorfer, Josef, Wuppertal, GERMANY, FEDERAL REPUBLIC OF
Perzborn, Elisabeth, Wuppertal, GERMANY, FEDERAL REPUBLIC OF
Pohlmann, Jens, Wuppertal, GERMANY, FEDERAL REPUBLIC OF
Rohrig, Susanne, Essen, GERMANY, FEDERAL REPUBLIC OF
Schlemmer, Karl-Heinz, Wuppertal, GERMANY, FEDERAL REPUBLIC OF

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 20040242660	A1	20041202	<--
	US 7767702	B2	20100803	
APPLICATION INFO.:	US 2004-481297	A1	20040628	(10)
	WO 2002-EP6237		20020607	

	NUMBER	DATE
PRIORITY INFORMATION:	DE 2001-10129725	20010620

DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: JEFFREY M. GREENMAN, BAYER PHARMACEUTICALS CORPORATION, 400 MORGAN LANE, WEST HAVEN, CT, 06516
NUMBER OF CLAIMS: 9
EXEMPLARY CLAIM: 1
LINE COUNT: 3139
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention relates to combinations of A) oxazolidinones of formula (I) and B) other active ingredients, to a method for producing said combinations and to the use thereof as medicaments, in particular for the treatment and/or prophylaxis of thrombo-embolic diseases. ##STR1##

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . reocclusions and restenoses after an angioplasty or aortocoronary bypass, stroke, transient ischemic attacks, peripheral arterial occlusive diseases, pulmonary embolisms or deep venous thromboses.
CLM What is claimed is:
. . . death, reocclusions and restenoses after angioplasty or aortocoronary bypass, stroke, transient ischemic attacks, peripheral arterial occlusive diseases, pulmonary embolisms or deep venous thromboses.

IT 348626-07-3DP, N-oxide 348626-08-4P 348626-17-5P 348626-20-0P
348626-21-1P 348626-22-2P 348626-23-3P 348626-24-4P
366789-02-8P 482305-66-8P 482305-67-9P 482305-68-0P
482305-69-1P 482305-70-4P 482305-71-5P 482305-72-6P 482305-73-7P
482305-74-8P 482305-75-9P 482305-76-0P 482305-77-1P 482305-78-2P
482305-79-3P 482305-80-6P 482305-82-8P 482305-83-9P 482305-84-0P
482305-85-1P 482305-87-3P 482305-88-4P 482305-89-5P 482305-90-8P
482305-91-9P 482305-92-0P 482306-30-9P 482306-32-1P 482306-33-2P
482306-49-0P 482306-50-3P 482306-58-1P 482306-62-7P 482306-63-8P
482306-64-9P 482306-65-0P 482306-66-1P 482306-67-2P 482306-68-3P
482306-69-4P 482306-70-7P 482306-73-0P 482306-75-2P 482306-76-3P
482306-77-4P 482306-78-5P 482306-88-7P 482306-91-2P 482306-92-3P
482306-93-4P 482306-94-5P 482306-95-6P 482306-96-7P 482306-98-9P
482307-00-6P 482307-02-8P 482307-03-9P 482307-05-1P 482307-15-3P
482307-16-4P 482307-17-5P 482307-18-6P 482307-19-7P 482307-20-0P
482307-21-1P 482307-22-2P 482307-23-3P 482307-24-4P 482307-25-5P
482307-26-6P 482307-27-7P 482307-28-8P 482307-29-9P 482307-30-2P
482307-31-3P 482307-32-4P 482307-33-5P 482307-34-6P 482307-35-7P
482307-36-8P 482307-37-9P 482307-38-0P 482307-39-1P 482307-40-4P
482307-41-5P 482307-42-6P 482307-43-7P 482307-44-8P 482307-45-9P
482307-46-0P 482307-47-1P 482307-48-2P 482307-49-3P 482307-50-6P
482307-51-7P 482307-52-8P 482307-53-9P 482307-54-0P 482307-55-1P
482307-56-2P 482307-57-3P 482307-58-4P 482307-59-5P 482307-60-8P
482307-61-9P 482307-63-1P 482307-64-2P 482307-65-3P 482307-66-4P
482307-67-5P 482307-68-6P 482307-69-7P 482307-71-1P 482307-72-2P
482307-73-3P 482307-74-4P 482307-76-6P 482307-77-7P 482307-78-8P
482307-79-9P 482307-80-2P 482307-81-3P 482307-82-4P 482307-83-5P
482307-84-6P 482307-85-7P 482307-86-8P 482307-88-0P 482307-90-4P
482307-91-5P 482307-92-6P 482307-93-7P 482307-94-8P 482307-95-9P
482307-96-0P 482307-97-1P 482308-00-9P
(preparation and pharmacol. activity of; preparation of substituted oxazolidinones for combinational therapy in the treatment and/or prophylaxis of thromboembolic diseases)

L7 ANSWER 19 OF 21 USPATFULL on STN
ACCESSION NUMBER: 2003:220319 USPATFULL
TITLE: Substituted oxazolidinones and their in the field of blood coagulation

INVENTOR(S): Straub, Alexander, Wuppertal, GERMANY, FEDERAL REPUBLIC OF
Lampe, Thomas, Wuppertal, GERMANY, FEDERAL REPUBLIC OF
Pohlmann, Jens, Wuppertal, GERMANY, FEDERAL REPUBLIC OF
Rohrig, Susanne, Essen, GERMANY, FEDERAL REPUBLIC OF
Perzborn, Elisabeth, Wuppertal, GERMANY, FEDERAL REPUBLIC OF
Schlemmer, Karl-Heinz, Wuppertal, GERMANY, FEDERAL REPUBLIC OF
Pernerstorfer, Joseph, Wuppertal, GERMANY, FEDERAL REPUBLIC OF

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 20030153610	A1	20030814	<--
	US 7157456	B2	20070102	
APPLICATION INFO.:	US 2002-181051	A1	20020624	(10)
	WO 2000-EP12492		20001211	

	NUMBER	DATE
PRIORITY INFORMATION:	DE 1999-19962924	19991224

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: JEFFREY M. GREENMAN, VICE PRESIDENT, PATENTS AND LICENSING, BAYER CORPORATION, 400 MORGAN LANE, WEST HAVEN, CT, 06516
NUMBER OF CLAIMS: 15
EXEMPLARY CLAIM: 1
LINE COUNT: 3805
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention relates to the field of blood coagulation. Novel oxazolidinone derivatives of the general formula (I) ##STR1##

processes for their preparation and their use as medicinally active compounds for the prophylaxis and/or treatment of disorders are described.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . angina), reocclusions and restenoses after angioplasty or aortocoronary bypass, stroke, transitory ischaemic attacks, peripheral arterial occlusive disorders, pulmonary embolisms or deep venous thromboses; hereinbelow, these disorders are collectively also referred to as thromboembolic disorders. In addition, in the case of consumption coagulopathy,. . .

SUMM . . . angina), reocclusions and restenoses after angioplasty or aortocoronary bypass, stroke, transitory ischaemic attacks, peripheral arterial occlusive disorders, pulmonary embolisms or deep venous thromboses.

SUMM . . . angina), reocclusions and restenoses after angioplasty or aortocoronary bypass, stroke, transitory ischaemic attacks, peripheral arterial occlusion disorders, pulmonary embolisms or deep venous thromboses.

CLM What is claimed is:

. . . angina), reocclusions and restenoses after angioplasty or aorto-coronary bypass, stroke, transitory ischaemic attacks, peripheral arterial occlusive diseases, pulmonary embolisms or deep venous thromboses.

IT 348626-08-4P 348626-10-8P 348626-11-9P 348626-12-0P 348626-13-1P
348626-14-2P 348626-17-5P 348626-18-6P 348626-19-7P 348626-20-0P

348626-21-1P 348626-22-2P 348626-23-3P 348626-24-4P 348626-33-5P
348626-34-6P 348626-35-7P 348626-36-8P 348626-54-0P
366789-02-8P 482305-66-8P 482305-67-9P 482305-68-0P
482305-69-1P 482305-70-4P 482305-71-5P 482305-72-6P 482305-73-7P
482305-74-8P 482305-75-9P 482305-76-0P 482305-77-1P 482305-78-2P
482305-79-3P 482305-80-6P 482305-81-7P 482305-82-8P 482305-83-9P
482305-84-0P 482305-85-1P 482305-88-4P 482305-89-5P 482305-90-8P
482305-91-9P 482305-92-0P 482305-93-1P 482306-29-6P 482306-30-9P
482306-31-0P 482306-32-1P 482306-33-2P 482306-34-3P 482306-35-4P
482306-36-5P 482306-37-6P 482306-38-7P 482306-39-8P 482306-40-1P
482306-41-2P 482306-42-3P 482306-43-4P 482306-44-5P 482306-45-6P
482306-46-7P 482306-47-8P 482306-48-9P 482306-49-0P 482306-50-3P
482306-51-4P 482306-52-5P 482306-53-6P 482306-54-7P 482306-55-8P
482306-56-9P 482306-57-0P 482306-58-1P 482306-59-2P 482306-60-5P
482306-63-8P 482306-64-9P 482306-65-0P 482306-66-1P 482306-67-2P
482306-68-3P 482306-69-4P 482306-70-7P 482306-71-8P 482306-76-3P
482306-77-4P 482306-78-5P 482306-79-6P 482306-80-9P 482306-81-0P
482306-82-1P 482306-83-2P 482306-84-3P 482306-85-4P 482306-88-7P
482306-91-2P 482306-92-3P 482306-93-4P 482306-94-5P 482306-95-6P
482306-96-7P 482306-98-9P 482307-00-6P 482307-02-8P 482307-03-9P
482307-04-0P 482307-05-1P 482307-06-2P 482307-07-3P 482307-08-4P
482307-09-5P 482307-10-8P 482307-11-9P 482307-12-0P 482307-13-1P
482307-14-2P 482307-15-3P 482307-16-4P 482307-17-5P 482307-18-6P
482307-19-7P 482307-20-0P 482307-21-1P 482307-22-2P 482307-23-3P
482307-24-4P 482307-25-5P 482307-26-6P 482307-27-7P 482307-28-8P
482307-29-9P 482307-30-2P 482307-31-3P 482307-32-4P 482307-33-5P
482307-34-6P 482307-35-7P 482307-36-8P 482307-37-9P 482307-38-0P
482307-39-1P 482307-40-4P 482307-41-5P 482307-42-6P 482307-43-7P
482307-44-8P 482307-45-9P 482307-46-0P 482307-47-1P 482307-48-2P
482307-49-3P 482307-50-6P 482307-51-7P 482307-52-8P 482307-53-9P
482307-54-0P 482307-55-1P 482307-56-2P 482307-57-3P 482307-58-4P
482307-59-5P 482307-60-8P 482307-61-9P 482307-63-1P 482307-64-2P
482307-65-3P 482307-66-4P 482307-67-5P 482307-68-6P 482307-69-7P
482307-71-1P 482307-72-2P 482307-73-3P 482307-74-4P 482307-76-6P
482307-77-7P 482307-78-8P 482307-79-9P 482307-80-2P 482307-81-3P
482307-82-4P 482307-83-5P 482307-84-6P 482307-85-7P 482307-86-8P
482307-88-0P 482307-90-4P 482307-91-5P 482307-92-6P 482307-93-7P
482307-94-8P 482307-95-9P 482307-96-0P 482307-97-1P 482307-98-2P
482308-00-9P 1008526-99-5P 1008527-02-3P 1008527-04-5P
1008527-05-6P
(preparation of substituted oxazolidinones for use in treatment of disorders associated with blood coagulation)

L7 ANSWER 20 OF 21 USPAT2 on STN
ACCESSION NUMBER: 2004:307984 USPAT2
TITLE: Substituted oxazolidinones for combinational therapy
INVENTOR(S): Straub, Alexander, Wuppertal, GERMANY, FEDERAL REPUBLIC OF
Lampe, Thomas, Dusseldorf, GERMANY, FEDERAL REPUBLIC OF
Pernerstorfer, Josef, Wuppertal, GERMANY, FEDERAL REPUBLIC OF
Perzborn, Elisabeth, Wuppertal, GERMANY, FEDERAL REPUBLIC OF
Pohlmann, Jens, Wuppertal, GERMANY, FEDERAL REPUBLIC OF
Rohrig, Susanne, Essen, GERMANY, FEDERAL REPUBLIC OF
Schlemmer, Karl-Heinz, Wuppertal, GERMANY, FEDERAL REPUBLIC OF
PATENT ASSIGNEE(S): Bayer Schering Pharma Aktiengesellschaft, GERMANY, FEDERAL REPUBLIC OF (non-U.S. corporation)

NUMBER	KIND	DATE

PATENT INFORMATION: US 7767702 B2 20100803
WO 2003000256 20030103 <--
APPLICATION INFO.: US 2002-481297 20020607 (10)
WO 2002-EP6237 20020607
20040628 PCT 371 date

	NUMBER	DATE
PRIORITY INFORMATION:	DE 2001-10129725	20010620

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Kwon, Brian-Yong S
LEGAL REPRESENTATIVE: Connolly Bove Lodge & Hutz, LLP
NUMBER OF CLAIMS: 4
EXEMPLARY CLAIM: 1
LINE COUNT: 3133
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention relates to combinations of A) oxazolidinones of formula (I) and B) other active ingredients, to a method for producing said combinations and to the use thereof as medicaments, in particular for the treatment and/or prophylaxis of thrombo-embolic diseases.

##STR1##

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . reocclusions and restenoses after an angioplasty or aortocoronary bypass, stroke, transient ischemic attacks, peripheral arterial occlusive diseases, pulmonary embolisms or deep venous thromboses.

IT 348626-07-3DP, N-oxide 348626-08-4P 348626-17-5P 348626-20-0P
348626-21-1P 348626-22-2P 348626-23-3P 348626-24-4P
366789-02-8P 482305-66-8P 482305-67-9P 482305-68-0P
482305-69-1P 482305-70-4P 482305-71-5P 482305-72-6P 482305-73-7P
482305-74-8P 482305-75-9P 482305-76-0P 482305-77-1P 482305-78-2P
482305-79-3P 482305-80-6P 482305-82-8P 482305-83-9P 482305-84-0P
482305-85-1P 482305-87-3P 482305-88-4P 482305-89-5P 482305-90-8P
482305-91-9P 482305-92-0P 482306-30-9P 482306-32-1P 482306-33-2P
482306-49-0P 482306-50-3P 482306-58-1P 482306-62-7P 482306-63-8P
482306-64-9P 482306-65-0P 482306-66-1P 482306-67-2P 482306-68-3P
482306-69-4P 482306-70-7P 482306-73-0P 482306-75-2P 482306-76-3P
482306-77-4P 482306-78-5P 482306-88-7P 482306-91-2P 482306-92-3P
482306-93-4P 482306-94-5P 482306-95-6P 482306-96-7P 482306-98-9P
482307-00-6P 482307-02-8P 482307-03-9P 482307-05-1P 482307-15-3P
482307-16-4P 482307-17-5P 482307-18-6P 482307-19-7P 482307-20-0P
482307-21-1P 482307-22-2P 482307-23-3P 482307-24-4P 482307-25-5P
482307-26-6P 482307-27-7P 482307-28-8P 482307-29-9P 482307-30-2P
482307-31-3P 482307-32-4P 482307-33-5P 482307-34-6P 482307-35-7P
482307-36-8P 482307-37-9P 482307-38-0P 482307-39-1P 482307-40-4P
482307-41-5P 482307-42-6P 482307-43-7P 482307-44-8P 482307-45-9P
482307-46-0P 482307-47-1P 482307-48-2P 482307-49-3P 482307-50-6P
482307-51-7P 482307-52-8P 482307-53-9P 482307-54-0P 482307-55-1P
482307-56-2P 482307-57-3P 482307-58-4P 482307-59-5P 482307-60-8P
482307-61-9P 482307-63-1P 482307-64-2P 482307-65-3P 482307-66-4P
482307-67-5P 482307-68-6P 482307-69-7P 482307-71-1P 482307-72-2P
482307-73-3P 482307-74-4P 482307-76-6P 482307-77-7P 482307-78-8P
482307-79-9P 482307-80-2P 482307-81-3P 482307-82-4P 482307-83-5P
482307-84-6P 482307-85-7P 482307-86-8P 482307-88-0P 482307-90-4P
482307-91-5P 482307-92-6P 482307-93-7P 482307-94-8P 482307-95-9P
482307-96-0P 482307-97-1P 482308-00-9P
(preparation and pharmacol. activity of; preparation of substituted oxazolidinones for combinational therapy in the treatment and/or

prophylaxis of thromboembolic diseases)

L7 ANSWER 21 OF 21 USPAT2 on STN
ACCESSION NUMBER: 2003:220319 USPAT2
TITLE: Substituted oxazolidinones and their use in the field of blood coagulation
INVENTOR(S): Straub, Alexander, Wuppertal, GERMANY, FEDERAL REPUBLIC OF
Lampe, Thomas, Wuppertal, GERMANY, FEDERAL REPUBLIC OF
Pohlmann, Jens, Wuppertal, GERMANY, FEDERAL REPUBLIC OF
Rohrig, Susanne, Essen, GERMANY, FEDERAL REPUBLIC OF
Perzborn, Elisabeth, Wuppertal, GERMANY, FEDERAL REPUBLIC OF
Schlemmer, Karl-Heinz, Wuppertal, GERMANY, FEDERAL REPUBLIC OF
Pernerstorfer, Joseph, Wuppertal, GERMANY, FEDERAL REPUBLIC OF
PATENT ASSIGNEE(S): Bayer HealthCare AG, Leverkusen, GERMANY, FEDERAL REPUBLIC OF (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 7157456	B2	20070102	
	WO 2001047919		20010705	<--
APPLICATION INFO.:	US 2000-181051		20001211	(10)
	WO 2000-EP12492		20001211	
			20020624	PCT 371 date

	NUMBER	DATE
PRIORITY INFORMATION:	DE 1999-19962924	19991224

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Saeed, Kamal A.
ASSISTANT EXAMINER: Anderson, Rebecca
LEGAL REPRESENTATIVE: Connolly Bove Lodge & Hutz LLP
NUMBER OF CLAIMS: 30
EXEMPLARY CLAIM: 1
LINE COUNT: 3611
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention relates to the field of blood coagulation. Novel oxazolidinone derivatives of the general formula (I)

##STR1## processes for their preparation and their use as medicinally active compounds for the prophylaxis and/or treatment of disorders are described.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . angina), reocclusions and restenoses after angioplasty or aortocoronary bypass, stroke, transitory ischaemic attacks, peripheral arterial occlusive disorders, pulmonary embolisms or deep venous thromboses; hereinbelow, these disorders are collectively also referred to as thromboembolic disorders. In addition, in the case of consumption coagulopathy,. . .
SUMM . . . angina), reocclusions and restenoses after angioplasty or aortocoronary bypass, stroke, transitory ischaemic attacks, peripheral arterial occlusive disorders, pulmonary embolisms or deep venous thromboses.
SUMM . . . angina), reocclusions and restenoses after angioplasty or aortocoronary bypass, stroke, transitory ischaemic attacks, peripheral arterial occlusion disorders, pulmonary embolisms or deep

venous thromboses.

CLM What is claimed is:

. . . thereof an effective amount of a compound of claim 1, wherein the thromboembolic disorder is myocardial infarct, pulmonary embolism or deep venous thrombosis.

CLM What is claimed is:

24. A method for the treatment of myocardial infarct, pulmonary embolism or deep venous thrombosis comprising administering an effective amount of the composition of claim 17 to a patient in need thereof.

CLM What is claimed is:

26. A method for the treatment of myocardial infarct, pulmonary embolism or deep venous thrombosis comprising administering an effective amount of the composition of claim 18 to a patient in need thereof.

CLM What is claimed is:

30. A method for the treatment of myocardial infarct, pulmonary embolism or deep venous thrombosis comprising administering an effective amount of the composition of claim 28 to a patient in need thereof.

IT 348626-08-4P 348626-10-8P 348626-11-9P 348626-12-0P 348626-13-1P
348626-14-2P 348626-17-5P 348626-18-6P 348626-19-7P 348626-20-0P
348626-21-1P 348626-22-2P 348626-23-3P 348626-24-4P 348626-33-5P
348626-34-6P 348626-35-7P 348626-36-8P 348626-54-0P
366789-02-8P 482305-66-8P 482305-67-9P 482305-68-0P
482305-69-1P 482305-70-4P 482305-71-5P 482305-72-6P 482305-73-7P
482305-74-8P 482305-75-9P 482305-76-0P 482305-77-1P 482305-78-2P
482305-79-3P 482305-80-6P 482305-81-7P 482305-82-8P 482305-83-9P
482305-84-0P 482305-85-1P 482305-88-4P 482305-89-5P 482305-90-8P
482305-91-9P 482305-92-0P 482305-93-1P 482306-29-6P 482306-30-9P
482306-31-0P 482306-32-1P 482306-33-2P 482306-34-3P 482306-35-4P
482306-36-5P 482306-37-6P 482306-38-7P 482306-39-8P 482306-40-1P
482306-41-2P 482306-42-3P 482306-43-4P 482306-44-5P 482306-45-6P
482306-46-7P 482306-47-8P 482306-48-9P 482306-49-0P 482306-50-3P
482306-51-4P 482306-52-5P 482306-53-6P 482306-54-7P 482306-55-8P
482306-56-9P 482306-57-0P 482306-58-1P 482306-59-2P 482306-60-5P
482306-63-8P 482306-64-9P 482306-65-0P 482306-66-1P 482306-67-2P
482306-68-3P 482306-69-4P 482306-70-7P 482306-71-8P 482306-76-3P
482306-77-4P 482306-78-5P 482306-79-6P 482306-80-9P 482306-81-0P
482306-82-1P 482306-83-2P 482306-84-3P 482306-85-4P 482306-88-7P
482306-91-2P 482306-92-3P 482306-93-4P 482306-94-5P 482306-95-6P
482306-96-7P 482306-98-9P 482307-00-6P 482307-02-8P 482307-03-9P
482307-04-0P 482307-05-1P 482307-06-2P 482307-07-3P 482307-08-4P
482307-09-5P 482307-10-8P 482307-11-9P 482307-12-0P 482307-13-1P
482307-14-2P 482307-15-3P 482307-16-4P 482307-17-5P 482307-18-6P
482307-19-7P 482307-20-0P 482307-21-1P 482307-22-2P 482307-23-3P
482307-24-4P 482307-25-5P 482307-26-6P 482307-27-7P 482307-28-8P
482307-29-9P 482307-30-2P 482307-31-3P 482307-32-4P 482307-33-5P
482307-34-6P 482307-35-7P 482307-36-8P 482307-37-9P 482307-38-0P
482307-39-1P 482307-40-4P 482307-41-5P 482307-42-6P 482307-43-7P
482307-44-8P 482307-45-9P 482307-46-0P 482307-47-1P 482307-48-2P
482307-49-3P 482307-50-6P 482307-51-7P 482307-52-8P 482307-53-9P
482307-54-0P 482307-55-1P 482307-56-2P 482307-57-3P 482307-58-4P
482307-59-5P 482307-60-8P 482307-61-9P 482307-63-1P 482307-64-2P
482307-65-3P 482307-66-4P 482307-67-5P 482307-68-6P 482307-69-7P
482307-71-1P 482307-72-2P 482307-73-3P 482307-74-4P 482307-76-6P
482307-77-7P 482307-78-8P 482307-79-9P 482307-80-2P 482307-81-3P
482307-82-4P 482307-83-5P 482307-84-6P 482307-85-7P 482307-86-8P

482307-88-0P 482307-90-4P 482307-91-5P 482307-92-6P 482307-93-7P
482307-94-8P 482307-95-9P 482307-96-0P 482307-97-1P 482307-98-2P
482308-00-9P 1008526-99-5P 1008527-02-3P 1008527-04-5P
1008527-05-6P
(preparation of substituted oxazolidinones for use in treatment of disorders associated with blood coagulation)

=> END
ALL L# QUERIES AND ANSWER SETS ARE DELETED AT LOGOFF
LOGOFF? (Y)/N/HOLD:HOLD

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	137.27	146.09

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-0.87	-0.87

SESSION WILL BE HELD FOR 120 MINUTES
STN INTERNATIONAL SESSION SUSPENDED AT 21:29:24 ON 09 MAR 2011

PTO/SB/08B (01-08)
Approved for use through 03/31/2008. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	11/883,218
Filing Date	July 27, 2007
First Named Inventor	Frank Misselwitz
Art Unit	N/A
Examiner Name	Not Yet Assigned
Attorney Docket Number	11987-00042-US

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
/J.K./	AA*	US-7,157,456-B2	01-02-2007	Straub et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
/J.K./	BA	WO-99/06371-A1	02-11-1999	Zeneca Limited		
/J.K./	BB	WO-01/47919-A1	07-05-2001	Bayer Aktiengesellschaft		See US 7,157,456 B2

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. * CITE NO.: Those application(s) which are marked with an single asterisk (*) next to the Cite No. are not supplied (under 37 CFR 1.98(a)(2)(iii)) because that application was filed after June 30, 2003 or is available in the IFW. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]

Examiner Signature	/Jody Karol/	Date Considered	03/11/2011

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1]Applicant's unique citation designation number (optional). [2]Applicant is to place a check mark here if English language Translation is attached.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

BIB DATA SHEET

CONFIRMATION NO. 9960

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
11/883,218	07/16/2008 RULE	514	1627	11987-00042

APPLICANTS

Frank Misselwitz, Heidelberg, GERMANY;
Dagmar Kubitza, Ratingen, GERMANY;
Son-Mi Park, Wuppertal, GERMANY;
Klaus Wehling, Wuppertal, GERMANY;

**** CONTINUING DATA ***************************

This application is a 371 of PCT/EP06/00431 01/19/2006

**** FOREIGN APPLICATIONS ***************************

EUROPEAN PATENT OFFICE (EPO) 05001893.6 01/31/2005

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****

09/18/2008

Foreign Priority claimed	35 USC 119(a-d) conditions met	Verified and Acknowledged	Met after Allowance	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
☑ Yes ☐ No	☑ Yes ☐ No	/Jody L. Karol/ Examiner's Signature	☐ Initials	GERMANY	0	8	3

ADDRESS

CONNOLLY BOVE LODGE & HUTZ, LLP
P O BOX 2207
WILMINGTON, DE 19899
UNITED STATES

TITLE

Prevention and Treatment of Thromboembolic Disorders

FILING FEE RECEIVED	FEES: Authority has been given in Paper	
1390	No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	39	(Misslewitz, Frank).in. or (Kubitza, Dagmar).in. or (Park, Son-Mi).in. or (Wehling, Klaus).in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2011/03/09 22:04
L2	122	BAY 59-7939	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2011/03/09 22:11
L3	242	rivaroxaban$3	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2011/03/09 22:11
L4	8750	(deep vein thrombos$2) or (deep venous thrombos$2)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2011/03/09 22:12
L5	1367	L4 and (Xa near3 inhibitor)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2011/03/09 22:13
L6	40	L4 and (direct factor Xa inhibitor)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2011/03/09 22:13
L7	55	L4 and ($thiophenecarboxamide)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2011/03/09 22:14
L8	227	514/230.8.ccls.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2011/03/09 22:23

L9	567	514/236.8.ccls.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2011/03/09 22:23
L10	53	L4 and (I8 or L9)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	ADJ	ON	2011/03/09 22:24

EAST Search History (Interference)

< This search history is empty>

3/9/2011 10:24:50 PM
C:\ Documents and Settings\ JKarol\ My Documents\ EAST\ Workspaces\ 11883218 - Prevention and Method of Treatment of Thromboembolic Disorders.wsp

356183

STIC Scientific and Technical Information Center

EIC 1600/2900

SEARCH REQUEST

SIRA Delivering Technologies to Patents

Today's Date 2/15/2011

Name Jody Karol

AU/Org. 1627 Examiner # 83987

Mailbox # Rem 4B11 Phone x03983

Priority App. Filing Date 1/31/2005

Case/App. # 11/883,218

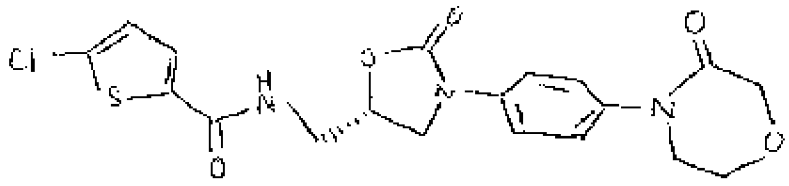
Format for Search Results

SCORE Email PAPER

Meaning of unusual acronyms or initialisms

Identify the novelty 5-chloro-N({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

Additional Comments/Drawings



Please submit completed form to your EIC.

STIC USE ONLY

Searcher

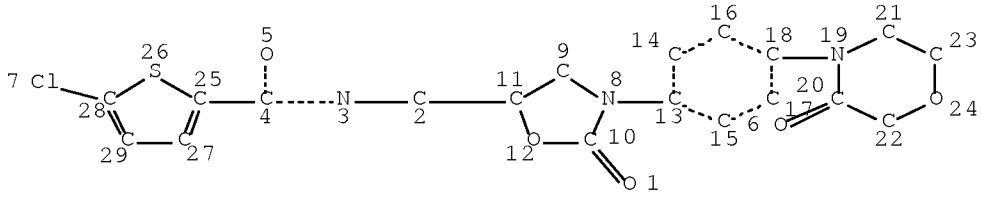
Date Completed

Phone

Sources

DISPLAY HISTORY

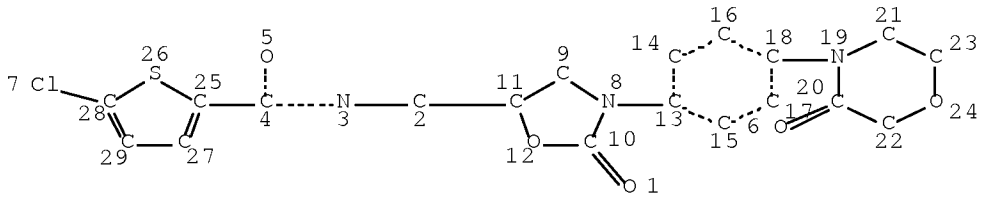
```
=> d his nofile l1-l6; d que stat l6; d his nofile l7-

     (FILE 'CAPLUS, MEDLINE, EMBASE' ENTERED AT 09:55:42 ON 17 FEB 2011)
L1             1 SEA SPE=ON  ABB=ON  PLU=ON  US2008-883218/AP


     FILE 'REGISTRY' ENTERED AT 10:30:55 ON 17 FEB 2011
L2             3 SEA SPE=ON  ABB=ON  PLU=ON  (366789-02-8/BI OR 679809-58-6/BI
                 OR 9002-05-5/BI)
                 D SCAN
L3             1 SEA SPE=ON  ABB=ON  PLU=ON  L2 AND C=19
                 D RN
L4               STR 366789-02-8
L5             2 SEA SSS SAM L4
                 D SCAN
                 D QUE
L6            32 SEA FAM FUL L4


L4               STR
```



```
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  29

STEREO ATTRIBUTES: NONE
L6            32 SEA FILE=REGISTRY FAM FUL L4

100.0% PROCESSED     249 ITERATIONS                                32 ANSWERS
SEARCH TIME: 00.00.01




     (FILE 'REGISTRY' ENTERED AT 10:30:55 ON 17 FEB 2011)
                 SAVE L6 TEMP KAROL/A
L7            52 SEA SPE=ON  ABB=ON  PLU=ON  D=0
L8           550 SEA SPE=ON  ABB=ON  PLU=ON  D<1
L9            20 SEA SPE=ON  ABB=ON  PLU=ON  L6 AND D/ELS
L10           12 SEA SPE=ON  ABB=ON  PLU=ON  L6 NOT L9
```

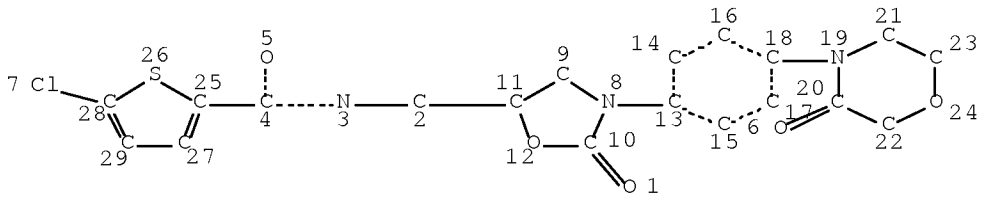
```
     FILE 'CAPLUS' ENTERED AT 10:34:15 ON 17 FEB 2011
L11          229 SEA SPE=ON  ABB=ON  PLU=ON  L6
L12          228 SEA SPE=ON  ABB=ON  PLU=ON  L10
L13          189 SEA SPE=ON  ABB=ON  PLU=ON  L11 (L) (THU OR PAC)/RL
L14         5813 SEA SPE=ON  ABB=ON  PLU=ON  (RAPID (3A) RELEAS?)/BI
L15            0 SEA SPE=ON  ABB=ON  PLU=ON  L14 AND L13
L16            0 SEA SPE=ON  ABB=ON  PLU=ON  L14 AND L11
L17       270925 SEA SPE=ON  ABB=ON  PLU=ON  DRUG DELIVER?/OBI
L18           86 SEA SPE=ON  ABB=ON  PLU=ON  L13 AND L17
L19       230417 SEA SPE=ON  ABB=ON  PLU=ON  (DAILY )/BI
L20           18 SEA SPE=ON  ABB=ON  PLU=ON  L19 AND L18
L21        46546 SEA SPE=ON  ABB=ON  PLU=ON  ORAL/OBI (L) L17
L22        31769 SEA SPE=ON  ABB=ON  PLU=ON  TABLET/OBI (L) L17
L23           68 SEA SPE=ON  ABB=ON  PLU=ON  L18 AND (L21 OR L22)
L24        76026 SEA SPE=ON  ABB=ON  PLU=ON  DOSAGE#/OBI
L25            0 SEA SPE=ON  ABB=ON  PLU=ON  L24 AND L23
L26            0 SEA SPE=ON  ABB=ON  PLU=ON  L18 AND L25
L27      1109302 SEA SPE=ON  ABB=ON  PLU=ON  DOS####/BI
L28           35 SEA SPE=ON  ABB=ON  PLU=ON  L27 AND L23
                 D KWIC
L29           52 SEA SPE=ON  ABB=ON  PLU=ON  MISSELWITZ F?/AU
L30           42 SEA SPE=ON  ABB=ON  PLU=ON  KUBITZA D?/AU
L31        39724 SEA SPE=ON  ABB=ON  PLU=ON  PARK S?/AU
L32           32 SEA SPE=ON  ABB=ON  PLU=ON  WEHLING K?/AU
L33        39843 SEA SPE=ON  ABB=ON  PLU=ON  (L29 OR L30 OR L31 OR L32)
L34           34 SEA SPE=ON  ABB=ON  PLU=ON  L33 AND L11
L35           20 SEA SPE=ON  ABB=ON  PLU=ON  L34 AND L19
                 D KWIC
L36           10 SEA SPE=ON  ABB=ON  PLU=ON  L35 AND ((L21 OR L22))
L37           13 SEA SPE=ON  ABB=ON  PLU=ON  L34 AND ((L21 OR L22))
L38           23 SEA SPE=ON  ABB=ON  PLU=ON  L37 OR L35
L39           34 SEA SPE=ON  ABB=ON  PLU=ON  L13 AND L19
L40           18 SEA SPE=ON  ABB=ON  PLU=ON  L39 AND ((L21 OR L22))
L41            9 SEA SPE=ON  ABB=ON  PLU=ON  L14 AND L33
L42            2 SEA SPE=ON  ABB=ON  PLU=ON  L41 AND ((L21 OR L22))
L43           25 SEA SPE=ON  ABB=ON  PLU=ON  L42 OR L38
L44            8 SEA SPE=ON  ABB=ON  PLU=ON  L30 AND ((L21 OR L22))
L45           38 SEA SPE=ON  ABB=ON  PLU=ON  L27 AND L18
L46           68 SEA SPE=ON  ABB=ON  PLU=ON  L13 AND ((L21 OR L22))
L47           35 SEA SPE=ON  ABB=ON  PLU=ON  L46 AND L27
L48           17 SEA SPE=ON  ABB=ON  PLU=ON  L47 AND L19
                 D KWIC
L49           16 SEA SPE=ON  ABB=ON  PLU=ON  L43 NOT L48
```

```
=> fil reg
FILE 'REGISTRY' ENTERED AT 10:58:18 ON 17 FEB 2011
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2011 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:   16 FEB 2011  HIGHEST RN 1263031-92-0
DICTIONARY FILE UPDATES:  16 FEB 2011  HIGHEST RN 1263031-92-0

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH June 26, 2010.

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document.  For information
on property searching in REGISTRY, refer to:

http://www.cas.org/support/stngen/stndoc/properties.html

=> d que stat l6
L4              STR
```



```
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  29

STEREO ATTRIBUTES: NONE
L6           32 SEA FILE=REGISTRY FAM FUL L4

100.0% PROCESSED     249 ITERATIONS                          32 ANSWERS
SEARCH TIME: 00.00.01


=> d que nos l10
L4              STR
L6           32 SEA FILE=REGISTRY FAM FUL L4
L9           20 SEA FILE=REGISTRY SPE=ON  ABB=ON  PLU=ON  L6 AND D/ELS
L10          12 SEA FILE=REGISTRY SPE=ON  ABB=ON  PLU=ON  L6 NOT L9
```

```
=> fil caplus
FILE 'CAPLUS' ENTERED AT 10:58:39 ON 17 FEB 2011
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2011 AMERICAN CHEMICAL SOCIETY (ACS)


Copyright of the articles to which records in this database refer is
held by the publishers listed in the PUBLISHER (PB) field (available
for records published or updated in Chemical Abstracts after December
26, 1996), unless otherwise indicated in the original publications.
The CA Lexicon is the copyrighted intellectual property of the
American Chemical Society and is provided to assist you in searching
databases on STN.  Any dissemination, distribution, copying, or storing
of this information, without the prior written consent of CAS, is
strictly prohibited.

FILE COVERS 1907 - 17 Feb 2011  VOL 154 ISS 8
FILE LAST UPDATED: 16 Feb 2011  (20110216/ED)
REVISED CLASS FIELDS (/NCL) LAST RELOADED:  Oct 2010
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE:  Oct 2010

CAplus now includes complete International Patent Classification (IPC)
reclassification data for the fourth quarter of 2010.

CAS Information Use Policies apply and are available at:

http://www.cas.org/legal/infopolicy.html

This file contains CAS Registry Numbers for easy and accurate
substance identification.
'OBI' IS DEFAULT SEARCH FIELD FOR 'CAPLUS' FILE

=> d que l48
L4              STR
```



```
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  29

STEREO ATTRIBUTES: NONE
L6            32 SEA FILE=REGISTRY FAM FUL L4
L11          229 SEA FILE=CAPLUS SPE=ON  ABB=ON  PLU=ON  L6
L13          189 SEA FILE=CAPLUS SPE=ON  ABB=ON  PLU=ON  L11 (L) (THU OR
```

```
                PAC)/RL
L17       270925 SEA FILE=CAPLUS SPE=ON  ABB=ON  PLU=ON  DRUG DELIVER?/OBI
L19       230417 SEA FILE=CAPLUS SPE=ON  ABB=ON  PLU=ON  (DAILY )/BI
L21        46546 SEA FILE=CAPLUS SPE=ON  ABB=ON  PLU=ON  ORAL/OBI (L) L17
L22        31769 SEA FILE=CAPLUS SPE=ON  ABB=ON  PLU=ON  TABLET/OBI (L) L17
L27      1109302 SEA FILE=CAPLUS SPE=ON  ABB=ON  PLU=ON  DOS####/BI
L46           68 SEA FILE=CAPLUS SPE=ON  ABB=ON  PLU=ON  L13 AND ((L21 OR L22))

L47           35 SEA FILE=CAPLUS SPE=ON  ABB=ON  PLU=ON  L46 AND L27
L48           17 SEA FILE=CAPLUS SPE=ON  ABB=ON  PLU=ON  L47 AND L19


=> d .ca hitstr l48 1-17

L48  ANSWER 1 OF 17  CAPLUS  COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER:         2010:291382  CAPLUS  Full-text
DOCUMENT NUMBER:          153:325499
TITLE:                    Rivaroxaban-Once daily, oral, direct factor
                          Xa inhibition Compared with vitamin K antagonism for
                          prevention of stroke and Embolism Trial in Atrial
                          Fibrillation: Rationale and Design of the ROCKET AF
                          study
CORPORATE SOURCE:         The Executive Steering Committee, Duke Clinical
                          Research Institute, Durham, NC, USA; Rocket AF Study
                          Investigators
SOURCE:                   American Heart Journal (2010), 159(3), 340-347
                          CODEN: AHJOA2; ISSN: 0002-8703
PUBLISHER:                Elsevier
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
ED   Entered STN:  10 Mar 2010
AB    Background: Atrial fibrillation (AF), the most common significant cardiac
      arrhythmia, increases the risk of stroke, particularly in the elderly.
      Warfarin is effective in reducing stroke risk but is burdensome to patients
      and is difficult to control.  Rivaroxaban is an oral direct factor Xa
      inhibitor in advanced development as an alternative to warfarin for the
      prevention and treatment of thromboembolic disorders.  Methods: ROCKET AF is a
      randomized, double-blind, double-dummy, event-driven trial, which aims to
      establish the noninferiority of rivaroxaban compared with warfarin in patients
      with nonvalvular AF who have a history of stroke or at least 2 addnl.
      independent risk factors for future stroke.  Patients are randomly assigned to
      receive rivaroxaban, 20 mg once daily (od), or dose-adjusted warfarin titrated
      to a target international normalized ratio (INR) of 2.5 (range 2.0-3.0,
      inclusive) using point-of-care INR devices to receive true or sham INR values,
      depending on the study drug allocation.  The primary efficacy end point is a
      composite of all-cause stroke and noncentral nervous system systemic embolism.
      The primary safety end point is the composite of major and clin. relevant
      nonmajor bleeding events.  Over 14,000 patients have been randomized at 1,100
      sites across 45 countries, and will be followed until 405 primary outcome
      events are observed  Conclusion: The ROCKET AF study will determine the
      efficacy and safety of rivaroxaban as an alternative to warfarin for the
      prevention of thromboembolism in patients with AF.
CC   1-8 (Pharmacology)
     Section cross-reference(s): 63
IT   Aging, animal
        (elderly; study was designed to show noninferiority of once
        daily rivaroxaban to warfarin in reducing combined endpoint of
        stroke, nervous system systemic embolism and inhibiting bleeding in
        patient with nonvalvular atrial fibrillation)
IT   Anticoagulants
```

Atrial fibrillation
Central nervous system
Human
Oral drug delivery systems
Stroke
(study was designed to show noninferiority of once daily rivaroxaban to warfarin in reducing combined endpoint of stroke, nervous system systemic embolism and inhibiting bleeding in patient with nonvalvular atrial fibrillation)

IT Embolism
(systemic; study was designed to show noninferiority of once daily rivaroxaban to warfarin in reducing combined endpoint of stroke, nervous system systemic embolism and inhibiting bleeding in patient with nonvalvular atrial fibrillation)

IT 12001-79-5, Vitamin K
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(antagonist; study was designed to show noninferiority of once daily rivaroxaban to warfarin in reducing combined endpoint of stroke, nervous system systemic embolism and inhibiting bleeding in patient with nonvalvular atrial fibrillation)

IT 9002-05-5, Factor Xa
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitor; study was designed to show noninferiority of once daily rivaroxaban to warfarin in reducing combined endpoint of stroke, nervous system systemic embolism and inhibiting bleeding in patient with nonvalvular atrial fibrillation)

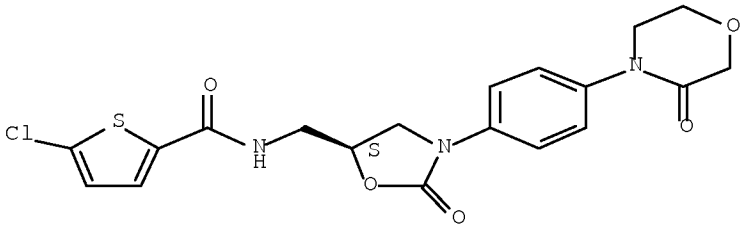
IT 366789-02-8, Rivaroxaban
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(study was designed to show noninferiority of once daily rivaroxaban to warfarin in reducing combined endpoint of stroke, nervous system systemic embolism and inhibiting bleeding in patient with nonvalvular atrial fibrillation)

IT 81-81-2, Warfarin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(study was designed to show noninferiority of once daily rivaroxaban to warfarin in reducing combined endpoint of stroke, nervous system systemic embolism and inhibiting bleeding in patient with nonvalvular atrial fibrillation)

IT 366789-02-8, Rivaroxaban
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(study was designed to show noninferiority of once daily rivaroxaban to warfarin in reducing combined endpoint of stroke, nervous system systemic embolism and inhibiting bleeding in patient with nonvalvular atrial fibrillation)

RN 366789-02-8 CAPLUS
CN 2-Thiophenecarboxamide, 5-chloro-N-[[(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-5-oxazolidinyl]methyl]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)
REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L48 ANSWER 2 OF 17 CAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 2010:230355 CAPLUS Full-text
DOCUMENT NUMBER: 153:192282
TITLE: Rivaroxaban: A New Oral Factor Xa Inhibitor
AUTHOR(S): Perzborn, Elisabeth; Roehrig, Susanne; Straub, Alexander; Kubitza, Dagmar; Mueck, Wolfgang; Laux, Volker
CORPORATE SOURCE: Bayer Schering Pharma AG, Wuppertal, Germany
SOURCE: Arteriosclerosis, Thrombosis, and Vascular Biology (2010), 30(3), 376-381
CODEN: ATVBFA; ISSN: 1079-5642
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 24 Feb 2010
AB A review. Rivaroxaban is a direct inhibitor of factor Xa, a coagulation factor at a critical juncture in the blood coagulation pathway leading to thrombin generation and clot formation. It is selective for human factor Xa, for which it has > 10,000-fold greater selectivity than for other biol. relevant serine proteases (half-maximal inhibitory concentration [IC50], > 20 μmol/L). Rivaroxaban inhibits factor Xa in a concentration-dependent manner (inhibitory constant [Ki], 0.4 nmol/L) and binds rapidly (kinetic association rate constant [kon], 1.7 + 107 mol/L-1 s-1) and reversibly (kinetic dissociation rate constant [koff], 5 + 10-3 s-1). By inhibiting prothrombinase complex-bound (IC50, 2.1 nmol/L) and clot-associated factor Xa (IC50, 75 nmol/L), rivaroxaban reduces the thrombin burst during the propagation phase. In animal models of venous and arterial thrombosis, rivaroxaban showed dose-dependent antithrombotic activity. In healthy individuals, rivaroxaban was found to have predictable pharmacokinetics and pharmacodynamics across a 5- to 80-mg total daily dose range, inhibiting factor Xa activity and prolonging plasma clotting time. In phase III clin. trials, rivaroxaban regimens reduced rates of venous thromboembolism in patients after total hip or knee arthroplasty compared with enoxaparin regimens, without significant differences in rates of major bleeding, showing that rivaroxaban has a favorable benefit-to-risk profile.
CC 1-0 (Pharmacology)
IT Anticoagulants
Human
Oral drug delivery systems
(oral rivaroxaban showed antithrombotic activity in animal model of venous or arterial thrombosis and reduced rate of venous thromboembolism in patient after hip or knee arthroplasty)
IT 366789-02-8, Rivaroxaban

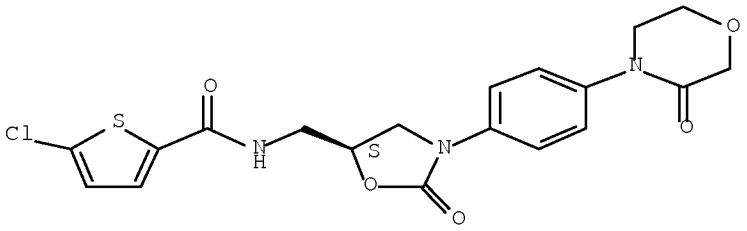
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral rivaroxaban showed antithrombotic activity in animal model of venous or arterial thrombosis and reduced rate of venous thromboembolism in patient after hip or knee arthroplasty)

IT 366789-02-8, Rivaroxaban
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral rivaroxaban showed antithrombotic activity in animal model of venous or arterial thrombosis and reduced rate of venous thromboembolism in patient after hip or knee arthroplasty)

RN 366789-02-8 CAPLUS

CN 2-Thiophenecarboxamide, 5-chloro-N-[[(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-5-oxazolidinyl]methyl]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 6 THERE ARE 6 CAPLUS RECORDS THAT CITE THIS RECORD (6 CITINGS)

REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L48 ANSWER 3 OF 17 CAPLUS COPYRIGHT 2011 ACS on STN

ACCESSION NUMBER: 2010:165012 CAPLUS Full-text

DOCUMENT NUMBER: 153:134308

TITLE: Safety, pharmacokinetics and pharmacodynamics of single doses of rivaroxaban - an oral, direct factor Xa inhibitor - in elderly Chinese subjects

AUTHOR(S): Jiang, Ji; Hu, Yufang; Zhang, Jianyan; Yang, Jueling; Mueck, Wolfgang; Kubitza, Dagmar; Bauer, Richard J.; Meng, Ling; Hu, Pei

CORPORATE SOURCE: The Clinical Pharmacology Research Center, Peking Union Medical College Hospital, Peop. Rep. China

SOURCE: Thrombosis and Haemostasis (2010), 103(1), 234-241
CODEN: THHADQ; ISSN: 0340-6245

PUBLISHER: Schattauer GmbH

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 09 Feb 2010

AB Rivaroxaban is a novel, oral, direct factor Xa (FXa) inhibitor for the prevention and treatment of thromboembolic disorders. The aim of this study was to investigate the safety, pharmacokinetics (PK) and pharmacodynamics (PD) of rivaroxaban in healthy, elderly Chinese subjects. In this single-center, single-blind, placebo-controlled, parallel-group, dose-escalation study, 79 subjects, aged 59-74 years (mean 62.8), were randomized to receive once-daily oral doses of rivaroxaban 5, 10, 20, 30 or 40 mg. Rivaroxaban was well tolerated: there was a low incidence of treatment-emergent adverse events and

all events were of mild intensity. Rivaroxaban was absorbed rapidly, reaching maximum plasma concns. within 2-4 h. The PK of rivaroxaban were dose dependent over the dose range tested. Maximal inhibition of FXa occurred 2-3 h after dosing and returned to baseline after 24-48 h, reflecting rivaroxaban plasma concns. Inhibition of FXa was associated with dose-dependent effects on global clotting tests. There were no clin. relevant differences in rivaroxaban plasma concns. between male and female subjects. In conclusion, rivaroxaban was well tolerated and was found to have predictable PK and PD in healthy, elderly Chinese subjects.

CC 1-2 (Pharmacology)

IT Human
Oral drug delivery systems
(oral rivaroxaban was tolerated and showed predictable pharmacokinetics and pharmacodynamics in healthy elderly Chinese human)

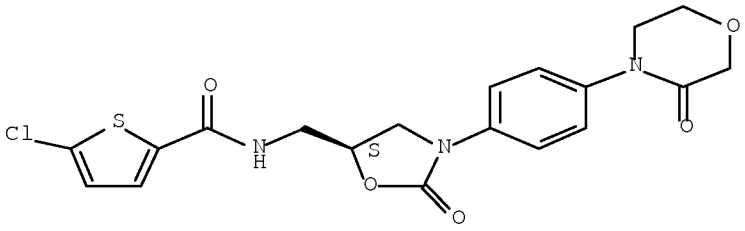
IT 366789-02-8, Rivaroxaban
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral rivaroxaban was tolerated and showed predictable pharmacokinetics and pharmacodynamics in healthy elderly Chinese human)

IT 366789-02-8, Rivaroxaban
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral rivaroxaban was tolerated and showed predictable pharmacokinetics and pharmacodynamics in healthy elderly Chinese human)

RN 366789-02-8 CAPLUS

CN 2-Thiophenecarboxamide, 5-chloro-N-[[(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-5-oxazolidinyl]methyl]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)

REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L48 ANSWER 4 OF 17 CAPLUS COPYRIGHT 2011 ACS on STN

ACCESSION NUMBER: 2009:1147818 CAPLUS Full-text

DOCUMENT NUMBER: 152:372349

TITLE: Rivaroxaban: a direct factor Xa inhibitor for VTE prophylaxis in patients undergoing total knee or hip replacement surgery

AUTHOR(S): Nunokawa, Nikki; Wong, Heather; Song, Jessica C.

CORPORATE SOURCE: University of the Pacific School of Pharmacy, Stockton, CA, USA

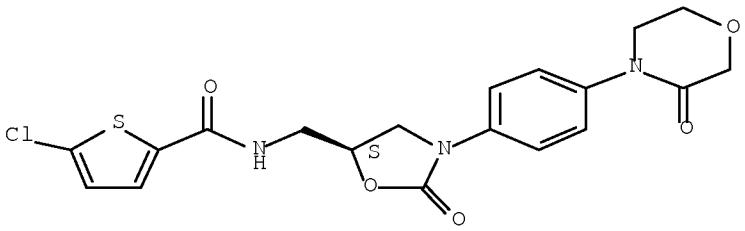
SOURCE: Formulary (2009), 44(8), 226-228, 231-236
CODEN: FORMF9; ISSN: 1082-801X

PUBLISHER: Advanstar Communications, Inc.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English
ED Entered STN: 21 Sep 2009
AB A review. Rivaroxaban is a highly potent direct factor Xa inhibitor with competitive and reversible activity that is pending FDA approval for the indication of venous thromboembolism (VTE) prophylaxis in patients undergoing total knee replacement (TKR) or total hip replacement (THR) surgery. Unlike the currently prescribed VTE prophylactic agents, which require s.c. administration or exhibit an undesirable drug interaction/monitoring profile, this agent offers the convenience of once- daily oral dosing, without the inconvenience of laboratory monitoring. In multiple phase 3 trials, rivaroxaban has demonstrated superior efficacy compared with enoxaparin in preventing VTE in patients undergoing THR and TKR, with comparable rates of major bleeding. The most commonly reported adverse events associated with rivaroxaban treatment include anemia, nausea, elevations in liver transaminases (short-term, with comparable incidence to that of enoxaparin), and postprocedural hemorrhage. Unresolved issues include the long-term hepatotoxicity profile of rivaroxaban and a potential risk of precipitating adverse cardiovascular events.
CC 1-0 (Pharmacology)
IT Drug interactions
(once-daily oral dosing of rivaroxaban did not show drug interaction and showed high efficacy in preventing venous thromboembolism prophylaxis in patient undergoing total knee or hip replacement surgery)
IT Human
Oral drug delivery systems
Prophylaxis
(once-daily oral dosing of rivaroxaban prevented venous thromboembolism prophylaxis in patient undergoing total knee or hip replacement surgery)
IT Surgery
(once-daily oral dosing of rivaroxaban prevented venous thromboembolism prophylaxis in patient undergoing total knee replacement surgery)
IT Embolism
Thrombosis
(thromboembolism; once-daily oral dosing of rivaroxaban prevented venous thromboembolism prophylaxis in patient undergoing total knee or hip replacement surgery)
IT 9002-05-5, Factor Xa
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitor; once-daily oral dosing of direct factor Xa inhibitor rivaroxaban prevented venous thromboembolism prophylaxis in patient undergoing total knee or hip replacement surgery)
IT 366789-02-8, Rivaroxaban
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(once-daily oral dosing of rivaroxaban prevented venous thromboembolism prophylaxis in patient undergoing total knee or hip replacement surgery)
IT 366789-02-8, Rivaroxaban
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(once-daily oral dosing of rivaroxaban prevented venous thromboembolism prophylaxis in patient undergoing total knee or hip replacement surgery)
RN 366789-02-8 CAPLUS
CN 2-Thiophenecarboxamide, 5-chloro-N-[[(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-5-oxazolidinyl]methyl]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

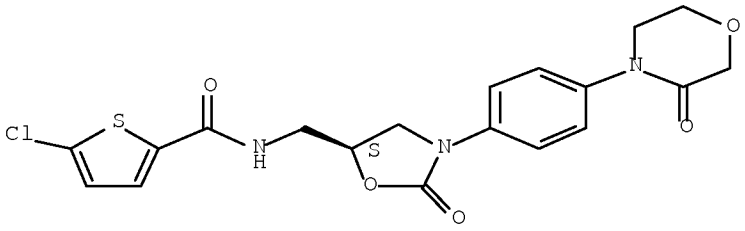


REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L48 ANSWER 5 OF 17 CAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 2009:1050428 CAPLUS Full-text
DOCUMENT NUMBER: 152:326187
TITLE: Safety, pharmacokinetics and pharmacodynamics of single/multiple doses of the oral, direct Factor Xa inhibitor rivaroxaban in healthy Chinese subjects
AUTHOR(S): Zhao, Xia; Sun, Peihong; Zhou, Ying; Liu, Yuwang; Zhang, Huilin; Mueck, Wolfgang; Kubitza, Dagmar; Bauer, Richard J.; Zhang, Hong; Cui, Yimin
CORPORATE SOURCE: Department of Pharmacy, Peking University First Hospital, Beijing, Peop. Rep. China
SOURCE: British Journal of Clinical Pharmacology (2009), 68(1), 77-88
CODEN: BCPHBM; ISSN: 0306-5251
PUBLISHER: Wiley-Blackwell
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 28 Aug 2009
AB To investigate the safety, pharmacokinetics and pharmacodynamics of rivaroxaban, an oral, direct Factor Xa (FXa) inhibitor, in healthy, male Chinese subjects. Two randomized, single-blind, placebo-controlled, dose-escalation studies were conducted in healthy Chinese men aged 18-45 years. In the single-dose study, subjects received single, oral doses of rivaroxaban 2.5, 5, 10, 20, and 40 mg. In the multiple-dose study, oral rivaroxaban was administered in doses of 5, 10, 20, and 30 mg twice daily for 6 days. Rivaroxaban, in single and multiple doses up to 60 mg, was well tolerated. Rapid absorption was observed in both studies (time to Cmax 1.25-2.5 h). In the multiple-dose study, rivaroxaban exposure increased dose-proportionally after the first dose and at steady state (for the 5-20-mg doses). The half-life of rivaroxaban was up to 7.9 h in the single-dose study. Maximal inhibition of FXa activity was achieved within 1-3 h of dosing in the single-dose study [at 20 mg FXa inhibition as a median percentage change from baseline, 45.92; 95% confidence interval (CI) 44.64, 50.70] and 2-3 h after administration at steady state in the multiple-dose study (at 20 mg median FXa inhibition as a median percentage change from baseline, 60.25; 95% CI 56.16, 63.05), in line with maximum rivaroxaban plasma concns. Rivaroxaban demonstrated predictable pharmacokinetics and pharmacodynamics in healthy Chinese subjects, in line with findings observed previously in White subjects. This suggests that fixed doses of rivaroxaban may be administered to all patients, regardless of their ethnic origin.
CC 1-2 (Pharmacology)
Section cross-reference(s): 63

IT Human
Oral drug delivery systems
Pharmacodynamics
Pharmacokinetics
(single/multiple doses of oral Xarelto was well tolerated and exhibited predictable pharmacokinetics, pharmacodynamics in healthy Chinese man)
IT 366789-02-8, Xarelto
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(single/multiple doses of oral Xarelto was well tolerated and exhibited predictable pharmacokinetics, pharmacodynamics in healthy Chinese man)
IT 9002-05-5, Factor Xa
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(single/multiple doses of oral direct factor Xa inhibitor Xarelto was well tolerated and exhibited predictable pharmacokinetics, pharmacodynamics in healthy Chinese man)
IT 366789-02-8, Xarelto
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(single/multiple doses of oral Xarelto was well tolerated and exhibited predictable pharmacokinetics, pharmacodynamics in healthy Chinese man)
RN 366789-02-8 CAPLUS
CN 2-Thiophenecarboxamide, 5-chloro-N-[[(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-5-oxazolidinyl]methyl]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

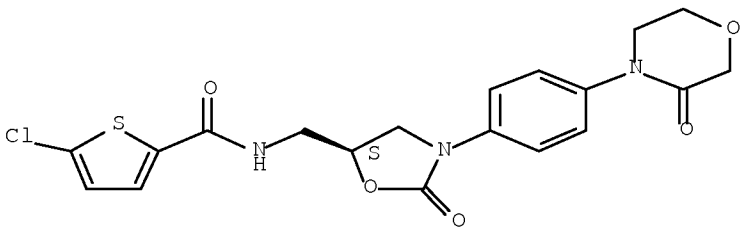


OS.CITING REF COUNT: 5 THERE ARE 5 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)
REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L48 ANSWER 6 OF 17 CAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 2009:725756 CAPLUS Full-text
DOCUMENT NUMBER: 152:110430
TITLE: Rivaroxaban for the prevention of venous thromboembolism following major orthopedic surgery: the RECORD trials
AUTHOR(S): Ageno, Walter
CORPORATE SOURCE: Department of Clinical Medicine, University of Insubria, Varese, Italy
SOURCE: Expert Review of Cardiovascular Therapy (2009), 7(6), 569-576
CODEN: ERCTAS; ISSN: 1477-9072
PUBLISHER: Expert Reviews Ltd.

DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 16 Jun 2009
AB A review. Patients undergoing total hip or knee arthroplasty face an increased risk for venous thromboembolism in the days and weeks following surgery. Hence, the routine application of prophylactic strategies is currently recommended. These include parenteral anticoagulants such as the low-mol.-weight heparins or fondaparinux and oral anticoagulants such as warfarin. New anticoagulant drugs are rapidly becoming available, including drugs that are administered orally, at fixed doses and without laboratory monitoring. Rivaroxaban is the first of a new class of anticoagulants: the selective, direct Factor Xa inhibitors. It has completed clin. evaluation in the setting of major orthopedic surgery and is now approved in many countries for the prevention of venous thromboembolism in patients undergoing total knee and hip arthroplasty. In this paper, we will review the trial data now supporting the clin. use of rivaroxaban and will discuss the potential role of this agent in daily clin. practice.
CC 1-0 (Pharmacology)
IT Oral drug delivery systems
(oral warfarin was effective for prevention of venous thromboembolism in patient undergoing total knee and hip arthroplasty)
IT 366789-02-8, Rivaroxaban
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(rivaroxaban was effective for prevention of venous thromboembolism in patient undergoing total knee and hip arthroplasty)
IT 366789-02-8, Rivaroxaban
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(rivaroxaban was effective for prevention of venous thromboembolism in patient undergoing total knee and hip arthroplasty)
RN 366789-02-8 CAPLUS
CN 2-Thiophenecarboxamide, 5-chloro-N-[[(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-5-oxazolidinyl]methyl]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L48 ANSWER 7 OF 17 CAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 2009:582061 CAPLUS Full-text
DOCUMENT NUMBER: 151:461961
TITLE: Rivaroxaban - an oral, direct Factor Xa inhibitor - lessons from a broad clinical study programme
AUTHOR(S): Haas, Sylvia

CORPORATE SOURCE: Institut fuer Experimentelle Onkologie und Therapieforschung, Technische Universitaet Muenchen, Munich, Germany
SOURCE: European Journal of Haematology (2009), 82(5), 339-349
CODEN: EJHAEC; ISSN: 0902-4441
PUBLISHER: Wiley-Blackwell
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 14 May 2009

AB A review. Anticoagulants are recommended for the prevention and treatment of venous thromboembolism (VTE), prevention of stroke in patients with atrial fibrillation (AF) and secondary prevention in patients with acute coronary syndrome (ACS). There is a clin. need for novel anticoagulants offering improvements over current standard of care, such as fixed oral dosing and no need for routine monitoring. Rivaroxaban, an oral, once-daily, direct Factor Xa inhibitor, has recently completed the RECORD phase III program for the prevention of VTE in patients undergoing total hip or knee replacement (THR or TKR), an indication for which it is approved in Europe and Canada. It is being investigated in large-scale phase III studies for VTE treatment and prevention of stroke in patients with AF, and phase III studies will soon commence for secondary prevention in patients with ACS. Phase I studies demonstrated that no routine anticoagulation monitoring was required, while phase II studies suggested that fixed daily doses had a wide therapeutic window. The four RECORD studies consistently showed that rivaroxaban was significantly more effective than enoxaparin in the prevention of VTE after THR and TKR, with a similar safety profile. This review describes the development of this novel anticoagulant, from bench to bedside.

CC 1-0 (Pharmacology)

IT Anticoagulants
Human
Oral drug delivery systems
(oral rivaroxaban was safe, effective without routine anticoagulation monitoring against venous thromboembolism in patient undergoing total hip or knee replacement and against stroke in patient with atrial fibrillation)

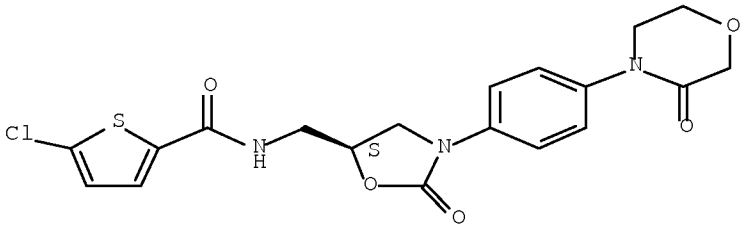
IT 366789-02-8, Rivaroxaban
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral rivaroxaban was safe, effective without routine anticoagulation monitoring against venous thromboembolism in patient undergoing total hip or knee replacement and against stroke in patient with atrial fibrillation)

IT 366789-02-8, Rivaroxaban
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral rivaroxaban was safe, effective without routine anticoagulation monitoring against venous thromboembolism in patient undergoing total hip or knee replacement and against stroke in patient with atrial fibrillation)

RN 366789-02-8 CAPLUS

CN 2-Thiophenecarboxamide, 5-chloro-N-[[(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-5-oxazolidinyl]methyl]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

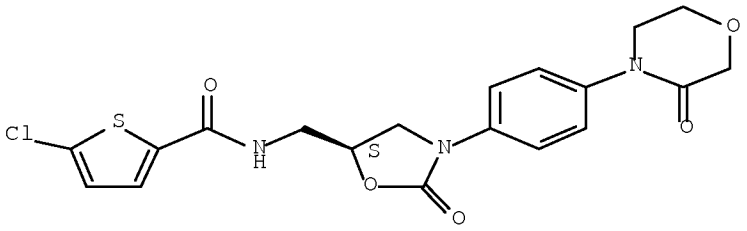


OS.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)
REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L48 ANSWER 8 OF 17 CAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 2009:435118 CAPLUS Full-text
DOCUMENT NUMBER: 151:417237
TITLE: Rivaroxaban, a new, oral, direct factor Xa inhibitor for thromboprophylaxis after major joint arthroplasty
AUTHOR(S): Borris, Lars C.
CORPORATE SOURCE: Department of Orthopaedics, Aarhus University Hospital, Aarhus C, DK-8000, Den.
SOURCE: Expert Opinion on Pharmacotherapy (2009), 10(6), 1083-1088
CODEN: EOPHF7; ISSN: 1465-6566
PUBLISHER: Informa Healthcare
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 13 Apr 2009
AB A review. The new oral, antithrombotic drug rivaroxaban is a direct factor Xa inhibitor, which can restrict thrombin generation both in vitro and in vivo. It has a predictable dose-dependent pharmacokinetic and pharmacodynamic profile and is well tolerated. In patients undergoing total hip or knee arthroplasty, rivaroxaban, 10 mg once daily started 6 - 8 h after the operation, had a significantly better antithrombotic efficacy and a comparable safety when compared with enoxaparin. Furthermore in all studies performed the drug had no adverse influence on the liver function in comparison with enoxaparin. In conclusion, rivaroxaban is a potent and safe new compound for antithrombotic prophylaxis in orthopedic surgery.
CC 1-0 (Pharmacology)
IT Anticoagulants
Human
Oral drug delivery systems
Pharmacodynamics
Pharmacokinetics
Prophylaxis
(rivaroxaban, a new, oral, direct factor Xa inhibitor for thromboprophylaxis after major joint arthroplasty)
IT 366789-02-8, Rivaroxaban 679809-58-6, Enoxaparin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(rivaroxaban, a new, oral, direct factor Xa inhibitor for thromboprophylaxis after major joint arthroplasty)
IT 366789-02-8, Rivaroxaban
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(rivaroxaban, a new, oral, direct factor Xa inhibitor for

thromboprophylaxis after major joint arthroplasty)
RN 366789-02-8 CAPLUS
CN 2-Thiophenecarboxamide, 5-chloro-N-[[(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-5-oxazolidinyl]methyl]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L48 ANSWER 9 OF 17 CAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 2009:351996 CAPLUS Full-text
DOCUMENT NUMBER: 150:555409
TITLE: Exploration of 4,4-disubstituted pyrrolidine-1,2-dicarboxamides as potent, orally active Factor Xa inhibitors with extended duration of action
AUTHOR(S): Van Huis, Chad A.; Casimiro-Garcia, Agustin; Bigge, Christopher F.; Cody, Wayne L.; Dudley, Danette A.; Filipski, Kevin J.; Heemstra, Ronald J.; Kohrt, Jeffrey T.; Leadley, Robert J.; Narasimhan, Lakshmi S.; McClanahan, Thomas; Mochalkin, Igor; Pamment, Michael; Thomas Peterson, J.; Sahasrabudhe, Vaishali; Schaum, Robert P.; Edmunds, Jeremy J.
CORPORATE SOURCE: Pfizer Global Research and Development, Michigan Laboratories, Ann Arbor, MI, 48105, USA
SOURCE: Bioorganic & Medicinal Chemistry (2009), 17(6), 2501-2511
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 150:555409
ED Entered STN: 24 Mar 2009
AB Aiming to improve upon previously disclosed Factor Xa inhibitors, a series of 4,4-disubstituted pyrrolidine-1,2-dicarboxamides were explored with the intent of increasing the projected human half-life vs. 5 (projected human t 1/2 = 6 h). A stereospecific route to compds. containing a 4-aryl-4-hydroxypyrrolidine scaffold was developed, resulting in several compds. that demonstrated an increase in the half-life as well as an increase in the in vitro potency compared to 5. Reported herein is the discovery of 26, containing a (2R,4S)-4-hydroxy-4-(2,4-difluorophenyl)- pyrrolidine scaffold, which is a selective, orally bioavailable, efficacious Factor Xa inhibitor that appears suitable for a once- daily dosing (projected human t 1/2 = 23 h).
CC 1-8 (Pharmacology)
IT Anticoagulants
Human
Oral drug delivery systems

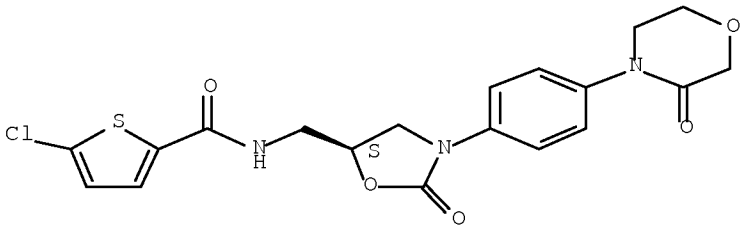
Thrombosis
(pyrrolidine dicarboxamides preparation as oral Factor Xa inhibitors with extended duration of action)

IT 211915-06-9, Dabigatran etexilate 313489-71-3, Ly517717
366789-02-8, Rivaroxaban 503612-47-3, Apixaban
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pyrrolidine dicarboxamides preparation as oral Factor Xa inhibitors with extended duration of action)

IT 366789-02-8, Rivaroxaban
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pyrrolidine dicarboxamides preparation as oral Factor Xa inhibitors with extended duration of action)

RN 366789-02-8 CAPLUS
CN 2-Thiophenecarboxamide, 5-chloro-N-[[(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-5-oxazolidinyl]methyl]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)
REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L48 ANSWER 10 OF 17 CAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 2008:1202821 CAPLUS Full-text
DOCUMENT NUMBER: 150:320442
TITLE: New compounds in the management of venous thromboembolism after orthopedic surgery: focus on rivaroxaban
AUTHOR(S): Borris, Lars Carl
CORPORATE SOURCE: Department of Orthopaedic Surgery, Aaarhus University Hospital, Aaarhus, Den.
SOURCE: Vascular Health and Risk Management (2008), 4(4), 855-862
CODEN: VHRMAT; ISSN: 1176-6344
PUBLISHER: Dove Medical Press (NZ) Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 07 Oct 2008
AB A review. Rivaroxaban (Xarelto) is a member of a new class of oral, direct (antithrombin-independent) factor Xa inhibitors, which restrict thrombin generation both in vitro and in vivo. After oral administration the absorption is near 100%, the bioavailability is near 80%, and the elimination half-life is 5-9 h with mixed excretion via the renal and fecal/biliary routes. The pharmacokinetics of rivaroxaban are predictable and consistent with a rapid onset of antithrombotic action within 2 h after administration. Phase 11 clin. studies have been carried out in patients undergoing total hip arthroplasty (THA) or total knee arthroplasty (TKA) and a dose of 10 mg once

daily for thromboprophylaxis was selected for further clin. development. The results of the phase III studies showed a significantly better antithrombotic efficacy of rivaroxaban compared with enoxaparin both in the short term (10–14 days) in TKA patients and long term (35 ± 4 days) in THA patients with a comparable safety. Symptomatic thromboembolic events were also significantly reduced with rivaroxaban. Liver enzyme elevation was seen in patients treated with rivaroxaban, but there was no indication of an increased risk of liver toxicity compared with enoxaparin. In conclusion, rivaroxaban is a potent and safe new compound for antithrombotic prophylaxis in orthopedic surgery.

CC 1-0 (Pharmacology)

IT Anticoagulants
Human
Oral drug delivery systems
Pharmacokinetics
(oral direct factor Xa inhibitor Xarelto restricted thrombin generation and it could be useful in treatment of venous thromboembolism in patient undergoing total hip and knee arthroplasty)

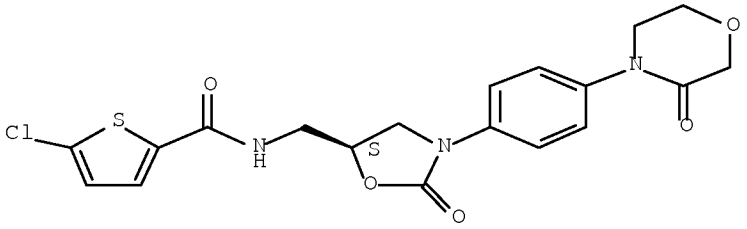
IT 366789-02-8, Xarelto
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral direct factor Xa inhibitor Xarelto restricted thrombin generation and it could be useful in treatment of venous thromboembolism in patient undergoing total hip and knee arthroplasty)

IT 366789-02-8, Xarelto
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral direct factor Xa inhibitor Xarelto restricted thrombin generation and it could be useful in treatment of venous thromboembolism in patient undergoing total hip and knee arthroplasty)

RN 366789-02-8 CAPLUS

CN 2-Thiophenecarboxamide, 5-chloro-N-[[(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-5-oxazolidinyl]methyl]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 5 THERE ARE 5 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L48 ANSWER 11 OF 17 CAPLUS COPYRIGHT 2011 ACS on STN

ACCESSION NUMBER: 2008:1112408 CAPLUS Full-text

DOCUMENT NUMBER: 150:182588

TITLE: Rivaroxaban: an oral direct inhibitor of factor Xa

AUTHOR(S): Gulseth, Michael P.; Michaud, Jessica; Nutescu, Edith A.

CORPORATE SOURCE: University of Minnesota College of Pharmacy, Duluth, USA

SOURCE: American Journal of Health-System Pharmacy (2008), 65(16), 1520-1529
CODEN: AHSPEK; ISSN: 1079-2082
PUBLISHER: American Society of Health-System Pharmacists
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 16 Sep 2008

AB A review. Purpose: The mechanism of action, pharmacodynamics, pharmacokinetics, efficacy in clin. trials, interactions, adverse effects and toxicity, and place in therapy of rivaroxaban are reviewed. Summary: Rivaroxaban, the first oral, direct factor Xa (FXa) inhibitor to reach Phase III trials, inhibits thrombin generation by both the intrinsic and the tissue factor pathways. It has shown predictable, reversible inhibition of FXa activity, and it may have the ability to inhibit clot-bound FXa. Rivaroxaban is being evaluated for prevention of venous thrombosis in patients undergoing hip or knee arthroplasty, treatment of venous thrombosis, long-term use for secondary prevention of venous thrombosis, and prevention of stroke in atrial fibrillation. To date, only short-term trials have been reported, but rivaroxaban's safety and efficacy appear to be at least equivalent to those of traditional anticoagulants. The results of four studies of primary prevention of venous thrombosis in patients undergoing orthopedic surgery suggest that rivaroxaban 10 mg daily is a promising alternative to low-mol.-weight heparins. Rivaroxaban appears to have a low potential for drug-drug or drug-food interactions. It offers the advantages of a fixed oral dose, rapid onset of action, and predictable and consistent anticoagulation effect, precluding the need for routine monitoring of anticoagulation. Conclusion: Rivaroxaban is a promising alternative to traditional anticoagulants for the prevention and treatment of venous thromboembolism and for stroke prevention in atrial fibrillation; it offers once-daily oral administration without the need for routine monitoring.

CC 1-0 (Pharmacology)

IT Anticoagulants
Atrial fibrillation
Drug interactions
Human
Oral drug delivery systems
Pharmacodynamics
Pharmacokinetics
(oral factor Xa inhibitor rivaroxaban for drug-drug or drug-food interaction was promising alternative to low-mol.-weight heparin for prevention and treatment of venous thromboembolism and stroke in atrial fibrillation in patient)

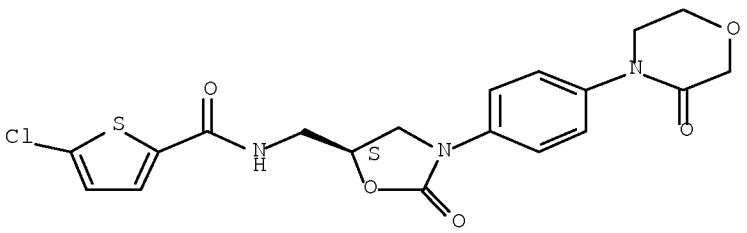
IT 366789-02-8, Rivaroxaban
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral factor Xa inhibitor rivaroxaban for drug-drug or drug-food interaction was promising alternative to low-mol.-weight heparin for prevention and treatment of venous thromboembolism and stroke in atrial fibrillation in patient)

IT 366789-02-8, Rivaroxaban
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral factor Xa inhibitor rivaroxaban for drug-drug or drug-food interaction was promising alternative to low-mol.-weight heparin for prevention and treatment of venous thromboembolism and stroke in atrial fibrillation in patient)

RN 366789-02-8 CAPLUS

CN 2-Thiophenecarboxamide, 5-chloro-N-[[(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-5-oxazolidinyl]methyl]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 9 THERE ARE 9 CAPLUS RECORDS THAT CITE THIS RECORD (9 CITINGS)
REFERENCE COUNT: 62 THERE ARE 62 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L48 ANSWER 12 OF 17 CAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 2008:831906 CAPLUS Full-text
DOCUMENT NUMBER: 150:15859
TITLE: Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial
AUTHOR(S): Kakkar, Ajay K.; Brenner, Benjamin; Dahl, Ola E.; Eriksson, Bengt I.; Mouret, Patrick; Muntz, Jim; Soglian, Andrea G.; Pap, Akos F.; Misselwitz, Frank; Haas, Sylvia
CORPORATE SOURCE: Barts and the London School of Medicine and Dentistry, London, E1 2AD, UK
SOURCE: Lancet (2008), 372(9632), 31-39
CODEN: LANCAO; ISSN: 0140-6736
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 10 Jul 2008
AB The risk of venous thromboembolism is high after total hip arthroplasty and could persist after hospital discharge. Our aim was to compare the use of rivaroxaban for extended thromboprophylaxis with short-term thromboprophylaxis with enoxaparin. Of the 2509 patients scheduled to undergo elective total hip arthroplasty were randomly assigned, stratified according to center, with a computer-generated randomization code, to receive oral rivaroxaban 10 mg once daily for 31-39 days (with placebo injection for 10-14 days; n = 1252), or enoxaparin 40 mg once daily s.c. for 10-14 days (with placebo tablet for 31-39 days; n = 1257). The primary efficacy outcome was the composite of deep-vein thrombosis (symptomatic or asymptomatic detected by mandatory, bilateral venog.), non-fatal pulmonary embolism, and all-cause mortality up to day 30-42. Analyses were done in the modified intention-to-treat population, which consisted of all patients who had received at least one dose of study medication, had undergone planned surgery, and had adequate assessment of thromboembolism. This study is registered at, number The modified intention-to-treat population for the anal. of the primary efficacy outcome consisted of 864 patients in the rivaroxaban group and 869 in the enoxaparin group. The primary outcome occurred in 17 (2.0%) patients in the rivaroxaban group, compared with 81 (9.3%) in the enoxaparin group (absolute risk reduction 7.3%, 95% CI 5.2-9.4; p < 0.0001). The incidence of any on-treatment bleeding was much the same in both groups (81 [6.6%] events in 1228 patients in the rivaroxaban safety population vs 68 [5.5%] of 1229 patients in the enoxaparin

safety population; p=0.25). Extended thromboprophylaxis with rivaroxaban was significantly more effective than short-term enoxaparin plus placebo for the prevention of venous thromboembolism, including symptomatic events, in patients undergoing total hip arthroplasty. Funding: Bayer HealthCare AG, Johnson & Johnson Pharmaceutical Research and Development LLC.

CC 1-8 (Pharmacology)

IT Anticoagulants
Arthroplasty
Human
Oral drug delivery systems
Prophylaxis
(extended thromboprophylaxis with oral Xarelto was significantly more effective than short-term s.c. Clexane for prevention of venous thromboembolism, including symptomatic events in patient undergone total hip arthroplasty)

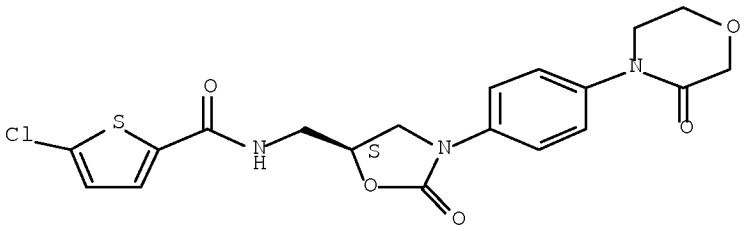
IT 366789-02-8, Xarelto 679809-58-6, Clexane
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(extended thromboprophylaxis with oral Xarelto was significantly more effective than short-term s.c. Clexane for prevention of venous thromboembolism, including symptomatic events in patient undergone total hip arthroplasty)

IT 366789-02-8, Xarelto
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(extended thromboprophylaxis with oral Xarelto was significantly more effective than short-term s.c. Clexane for prevention of venous thromboembolism, including symptomatic events in patient undergone total hip arthroplasty)

RN 366789-02-8 CAPLUS

CN 2-Thiophenecarboxamide, 5-chloro-N-[[(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-5-oxazolidinyl]methyl]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 89 THERE ARE 89 CAPLUS RECORDS THAT CITE THIS RECORD (89 CITINGS)

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L48 ANSWER 13 OF 17 CAPLUS COPYRIGHT 2011 ACS on STN

ACCESSION NUMBER: 2008:792274 CAPLUS Full-text

DOCUMENT NUMBER: 149:143645

TITLE: Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty

AUTHOR(S): Eriksson, Bengt I.; Borris, Lars C.; Friedman, Richard J.; Haas, Sylvia; Huisman, Menno V.; Kakkar, Ajay K.; Bandel, Tiemo J.; Beckmann, Horst; Muehlhofer, Eva;

Misselwitz, Frank; Geerts, William; Levine, M.; Eriksson, H.; Sandgren, G.; Wallin, J.; Bode, C.; Bassand, J. P.; Luscher, T.; Angeras, U.; Falk, A.; Prins, M.; Leizorovicz, A.; Bounameaux, H.; Larrey, D.; Migge, A.; Beckmann, H.; Muehlhofer, E.

CORPORATE SOURCE: RECORD1 Study Group, Sahlgrenska University Hospital-Ostra, Goeteborg, Swed.

SOURCE: New England Journal of Medicine (2008), 358(26), 2765-2775
CODEN: NEJMAG; ISSN: 0028-4793
PUBLISHER: Massachusetts Medical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 02 Jul 2008

AB This phase 3 trial compared the efficacy and safety of rivaroxaban, an oral direct inhibitor of factor Xa, with those of enoxaparin for extended thromboprophylaxis in patients undergoing total hip arthroplasty. In this randomized, double-blind study, we assigned 4541 patients to receive either 10 mg of oral rivaroxaban once daily, beginning after surgery, or 40 mg of enoxaparin s.c. once daily, beginning the evening before surgery, plus a placebo tablet or injection. The primary efficacy outcome was the composite of deep-vein thrombosis (either symptomatic or detected by bilateral venog. if the patient was asymptomatic), nonfatal pulmonary embolism, or death from any cause at 36 days (range, 30 to 42). The main secondary efficacy outcome was major venous thromboembolism (proximal deep-vein thrombosis, nonfatal pulmonary embolism, or death from venous thromboembolism). The primary safety outcome was major bleeding. A total of 3153 patients were included in the superiority anal. (after 1388 exclusions), and 4433 were included in the safety anal. (after 108 exclusions). The primary efficacy outcome occurred in 18 of 1595 patients (1.1%) in the rivaroxaban group and in 58 of 1558 patients (3.7%) in the enoxaparin group (absolute risk reduction, 2.6%; 95% confidence interval [CI], 1.5 to 3.7; P < 0.001). Major venous thromboembolism occurred in 4 of 1686 patients (0.2%) in the rivaroxaban group and in 33 of 1678 patients (2.0%) in the enoxaparin group (absolute risk reduction, 1.7%; 95% CI, 1.0 to 2.5; P < 0.001). Major bleeding occurred in 6 of 2209 patients (0.3%) in the rivaroxaban ban group and in 2 of 2224 patients (0.1%) in the enoxaparin group (P = 0.18). A once-daily , 10-mg oral dose of rivaroxaban was significantly more effective for extended thromboprophylaxis than a once-daily, 40-mg s.c. dose of enoxaparin in patients undergoing elective total hip arthroplasty. The two drugs had similar safety profiles.

CC 1-8 (Pharmacology)

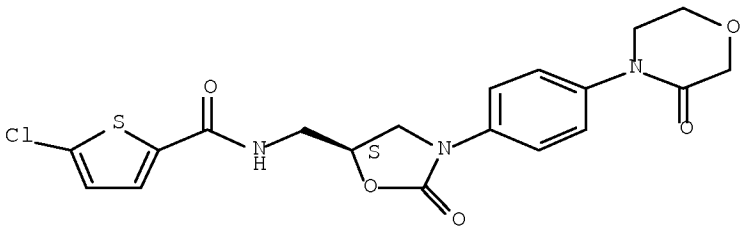
IT Anticoagulants
Arthroplasty
Drug toxicity
Hemorrhage
Hip
Human
Oral drug delivery systems
Prophylaxis
(rivaroxaban vs. enoxaparin for thromboprophylaxis after hip arthroplasty)

IT 366789-02-8, Xarelto 679809-58-6, Clexane
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study);
USES (Uses)
(rivaroxaban vs. enoxaparin for thromboprophylaxis after hip arthroplasty)

IT 366789-02-8, Xarelto
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study);

USES (Uses)
(rivaroxaban vs. enoxaparin for thromboprophylaxis after hip arthroplasty)
RN 366789-02-8 CAPLUS
CN 2-Thiophenecarboxamide, 5-chloro-N-[[(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-5-oxazolidinyl]methyl]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 109 THERE ARE 109 CAPLUS RECORDS THAT CITE THIS RECORD (109 CITINGS)
REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L48 ANSWER 14 OF 17 CAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 2008:531169 CAPLUS Full-text
DOCUMENT NUMBER: 149:44772
TITLE: Population pharmacokinetics and pharmacodynamics of rivaroxaban - an oral, direct factor Xa inhibitor - in patients undergoing major orthopaedic surgery
AUTHOR(S): Mueck, Wolfgang; Eriksson, Bengt I.; Bauer, Kenneth A.; Borris, Lars; Dahl, Ola E.; Fisher, William D.; Gent, Michael; Haas, Sylvia; Huisman, Menno V.; Kakkar, Ajay K.; Kaelebo, Peter; Kwong, Louis M.; Misselwitz, Frank; Turpie, Alexander G. G.
CORPORATE SOURCE: Bayer HealthCare AG, Wuppertal, Germany
SOURCE: Clinical Pharmacokinetics (2008), 47(3), 203-216
CODEN: CPKNDH; ISSN: 0312-5963
PUBLISHER: Wolters Kluwer Health
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 02 May 2008
AB Background: There is a clin. need for novel oral anticoagulants with predictable pharmacokinetics and pharmacodynamics. Rivaroxaban is an oral direct Factor Xa (FXa) inhibitor in clin. development for the prevention and treatment of thromboembolic disorders. This anal. was performed to characterize the population pharmacokinetics and pharmacodynamics of rivaroxaban in patients participating in two phase II, double-blind, randomized, active-comparator-controlled studies of twice-daily rivaroxaban for the prevention of venous thromboembolism after total hip- or knee-replacement surgery. Methods: Sparse blood samples were taken from all patients participating in the studies (n = 1009). In addition, a subset of patients in the hip study (n = 36) underwent full profiling. Rivaroxaban plasma concns., FXa activity and the prothrombin time were determined Nonlinear mixed-effects modeling was used to model the population pharmacokinetics and pharmacodynamics of rivaroxaban. Results: An oral one-compartment model described the population pharmacokinetics of rivaroxaban well. On the first postoperative day only, categorization of patients as slow

or fast absorbers as a tool to address variability in absorption improved the fit of the model. Clearance of rivaroxaban was lower and more variable on the first postoperative day, and so time was factored into the model. Overall, the only major difference between the models for the hip study and the knee study was that clearance was 26% lower in the knee study, resulting in approx. 30% higher exposure. Residual variability in the models was moderate (37% and 34% in the hip and knee studies, resp.). Plasma concns. of rivaroxaban increased dose dependently. Pharmacokinetic parameters that were estimated using the models agreed closely with results from full-profile patients in the hip study, demonstrating that rivaroxaban pharmacokinetics are predictable. The pharmacokinetics of rivaroxaban were affected by expected covariates: age affected clearance in the hip study only, hematocrit (on the first postoperative day only) and gender affected clearance in the knee study only, and renal function affected clearance in both studies. Bodyweight affected the volume of distribution in both studies. However, the effects of covariates on the pharmacokinetics of rivaroxaban were generally small, and predictions of 'extreme' case scenarios suggested that fixed dosing of rivaroxaban was likely to be possible. FXa activity and the prothrombin time were both affected by surgery, probably because of perioperative bleeding and i.v. administration of fluids; therefore, time was included in the pharmacodynamic models. In both studies, FXa activity correlated with rivaroxaban plasma concns. following a maximum effect model, whereas prothrombin time prolongation correlated following a linear model with intercept. The slope of the prothrombin time prolongation correlation was 3.2 s/(100 μg/L) in the hip study and 4.2 s/(100 μg/L) in the knee study. Both pharmacodynamic models in both studies demonstrated low residual variability of approx. 10%. Conclusion: This population anal. in patients undergoing major orthopedic surgery demonstrated that rivaroxaban has predictable, dose-dependent pharmacokinetics that were well described by an oral one-compartment model and affected by expected covariates. Rivaroxaban exposure could be assessed using the prothrombin time, if necessary, but not the international normalized ratio. The findings suggested that fixed dosing of rivaroxaban may be possible in patients undergoing major orthopedic surgery.

CC 1-8 (Pharmacology)

IT Artificial joint
(artificial hip; oral rivaroxaban showed predictable, dose-dependent pharmacokinetic profile and low residual variability which was affected by covariate age of patient of Europe, United States undergoing major hip-replacement surgery)

IT Artificial joint
Knee
(artificial knee; oral rivaroxaban showed dose-dependent decrease in pharmacokinetic drug clearance which was affected by covariate gender of patient of Europe, United States undergoing major knee-replacement surgery)

IT Hip
(artificial; oral rivaroxaban showed predictable, dose-dependent pharmacokinetic profile and low residual variability which was affected by covariate age of patient of Europe, United States undergoing major hip-replacement surgery)

IT Anticoagulants
(oral anticoagulant rivaroxaban had predictable, dose-dependent pharmacokinetic profile, low residual variability which was affected by covariates in patient of Europe, US undergoing major hip- or knee-replacement surgery)

IT Albumins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(oral rivaroxaban showed dose-dependent pharmacokinetic profile, low residual variability while serum albumin was related with decrease in prothrombin time in patient of Europe, United States

undergoing major hip- or knee-replacement surgery)

IT Aging, animal
(oral rivaroxaban showed predictable, dose-dependent pharmacokinetic profile and low residual variability which was affected by covariate age of patient of Europe, United States undergoing major hip-replacement surgery)

IT Body weight
(oral rivaroxaban showed predictable, dose-dependent pharmacokinetic profile and low residual variability which was affected by covariate body weight in patient of Europe, United States undergoing major hip- or knee-replacement surgery)

IT Sex
(oral rivaroxaban showed predictable, dose-dependent pharmacokinetic profile and low residual variability which was affected by covariate gender of patient of Europe, United States undergoing major knee-replacement surgery)

IT Human
Human groups
Oral drug delivery systems
Pharmacodynamics
Pharmacokinetics
(oral rivaroxaban showed predictable, dose -dependent pharmacokinetic profile, low residual variability which was affected by covariate body weight, renal function in patient of Europe, US undergoing major hip- or knee-replacement surgery)

IT Hematocrit
(oral rivaroxaban showed predictable, dose-dependent pharmacokinetic profile, low residual variability which was affected by covariate hematocrit value in patient of Europe, United States undergoing major hip- or knee-replacement surgery)

IT Surgery
(orthopedic; oral rivaroxaban showed predictable, dose -dependent pharmacokinetic profile, low residual variability which was affected by covariate body weight, renal function in patient of Europe, US undergoing major hip- or knee-replacement surgery)

IT Embolism
Thrombosis
(thromboembolism; oral rivaroxaban for prevention of venous thromboembolism showed predictable, dose-dependent pharmacokinetic profile and low residual variability in patient of Europe, United States undergoing major hip- or knee-replacement surgery)

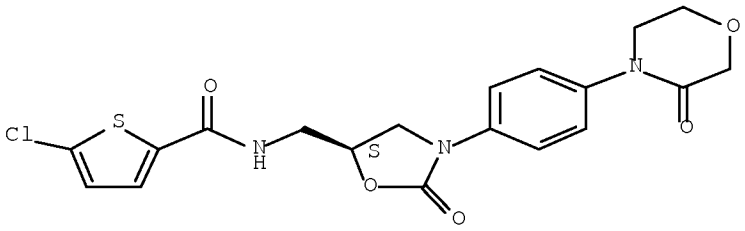
IT 9002-05-5, Factor Xa
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitor; oral factor Xa inhibitor rivaroxaban showed predictable, dose-dependent pharmacokinetic profile, low residual variability which was affected by covariates in patient of Europe, US undergoing major hip- or knee-replacement surgery)

IT 60-27-5, Creatinine
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(oral rivaroxaban had dose-dependent pharmacokinetic profile, low residual variability while creatinine clearance level was related with increase in prothrombin time in patient of Europe, US undergoing major hip- or knee-replacement surgery)

IT 366789-02-8, Rivaroxaban
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral rivaroxaban showed predictable, dose-dependent pharmacokinetic profile, low residual variability which was affected by covariate body weight, renal function in patient of Europe, US undergoing

major hip- or knee-replacement surgery)
IT 366789-02-8, Rivaroxaban
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral rivaroxaban showed predictable, dose-dependent pharmacokinetic profile, low residual variability which was affected by covariate body weight, renal function in patient of Europe, US undergoing major hip- or knee-replacement surgery)
RN 366789-02-8 CAPLUS
CN 2-Thiophenecarboxamide, 5-chloro-N-[[(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-5-oxazolidinyl]methyl]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 31 THERE ARE 31 CAPLUS RECORDS THAT CITE THIS RECORD (31 CITINGS)
REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L48 ANSWER 15 OF 17 CAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 2007:820415 CAPLUS Full-text
DOCUMENT NUMBER: 147:291299
TITLE: Population model of the pharmacokinetics and pharmacodynamics of rivaroxaban - an oral, direct Factor Xa inhibitor - in healthy subjects
AUTHOR(S): Mueck, W.; Becka, M.; Kubitza, D.; Voith, B.; Zuehlsdorf, M.
CORPORATE SOURCE: Clinical Pharmacology, Bayer HealthCare AG, Wuppertal, Germany
SOURCE: International Journal of Clinical Pharmacology and Therapeutics (2007), 45(6), 335-344
CODEN: ICTHEK; ISSN: 0946-1965
PUBLISHER: Dustri-Verlag Dr. Karl Feistle
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 27 Jul 2007
AB Objective: Rivaroxaban (BAY 59-7939) is an oral, direct Factor Xa (FXa) inhibitor being developed for the prevention and treatment of thromboembolic disorders. This anal. aimed to define population models for the pharmacokinetics (PK) and pharmacodynamics (PD) of rivaroxaban in healthy males. Methods: Non-linear, mixed-effect modeling was used to analyze rivaroxaban plasma concentration and PD data (FXa activity and clotting tests) from subjects in a phase I, multiple-ascending-dose study. Subjects received 5 mg rivaroxaban once, twice or three times daily, or 10, 20 or 30 mg rivaroxaban twice daily. Results: The population PK of rivaroxaban were well described by an oral, two-compartment model with first-order absorption and elimination from the central compartment. Population mean ests. for apparent oral clearance and volume of distribution for the central compartment were 9.2

l/h and 551, resp., with moderate inter-individual variability (17.4% and 30.7%, resp.). Total volume of distribution for rivaroxaban at steady state was .apprx.70 l. Residual (unexplained) variability was 25%. FXa activity correlated with rivaroxaban plasma concns. following an inhibitory Emax model; prothrombin time (PT) and rivaroxaban plasma concns. correlated with a linear model, with a slope of 4.6 s/(100 μg/l). Inter-individual variability was low for the correlation with PT. The models derived were used to define sampling windows for population PK/PD modeling in Phase II studies. Conclusions: This anal. confirms that rivaroxaban has predictable, dose-proportional PK and PD. The linear correlation between rivaroxaban plasma concns. and PT suggests that this test might be useful to assess rivaroxaban exposure in patients, if required.

CC 1-2 (Pharmacology)

IT Human
Oral drug delivery systems
Pharmacodynamics
Pharmacokinetics
(population pharmacokinetics/pharmacodynamics model of rivaroxaban was defined, plasma concentration of rivaroxaban correlated with Factor Xa activity or prothrombin time and may be used to assess its exposure in human)

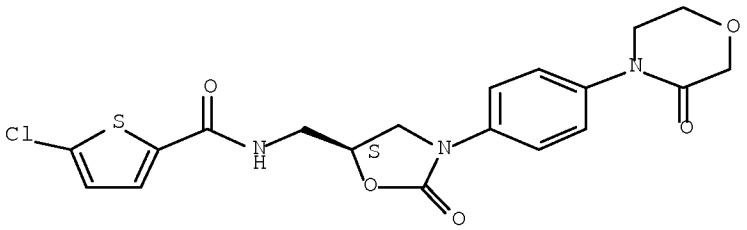
IT 366789-02-8, Rivaroxaban
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(population pharmacokinetics/pharmacodynamics model of rivaroxaban was defined, plasma concentration of rivaroxaban correlated with Factor Xa activity or prothrombin time and may be used to assess its exposure in human)

IT 366789-02-8, Rivaroxaban
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(population pharmacokinetics/pharmacodynamics model of rivaroxaban was defined, plasma concentration of rivaroxaban correlated with Factor Xa activity or prothrombin time and may be used to assess its exposure in human)

RN 366789-02-8 CAPLUS

CN 2-Thiophenecarboxamide, 5-chloro-N-[[(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-5-oxazolidinyl]methyl]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 27 THERE ARE 27 CAPLUS RECORDS THAT CITE THIS RECORD (27 CITINGS)

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

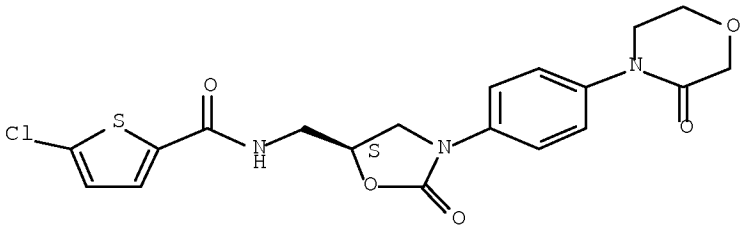
L48 ANSWER 16 OF 17 CAPLUS COPYRIGHT 2011 ACS on STN

ACCESSION NUMBER: 2007:731985 CAPLUS Full-text

DOCUMENT NUMBER: 147:419644
TITLE: Treatment of Proximal Deep-Vein Thrombosis with the Oral Direct Factor Xa Inhibitor Rivaroxaban (BAY 59-7939): The ODIXa-DVT (Oral Direct Factor Xa Inhibitor BAY 59-7939 in Patients with Acute Symptomatic Deep-Vein Thrombosis) Study
AUTHOR(S): Agnelli, Giancarlo; Gallus, Alexander; Goldhaber, Samuel Z.; Haas, Sylvia; Huisman, Menno V.; Hull, Russel D.; Kakkar, Ajay K.; Misselwitz, Frank; Schellong, Sebastian
CORPORATE SOURCE: ODIXa-DVT Study Investigators, Division of Internal and Cardiovascular Medicine-Stroke Unit, University of Perugia, Perugia, Italy
SOURCE: Circulation (2007), 116(2), 180-187
CODEN: CIRCAZ; ISSN: 0009-7322
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 06 Jul 2007
AB Background: An effective and safe oral anticoagulant that needs no monitoring for dose adjustment is urgently needed for the treatment of diseases that require long-term anticoagulation. Rivaroxaban (BAY 59-7939) is an oral direct factor Xa inhibitor currently under clin. development. Methods and Results: This randomized, parallel-group phase II trial in patients with proximal deep-vein thrombosis explored the efficacy and safety of rivaroxaban 10, 20, or 30 mg BID or 40 mg once daily compared with enoxaparin 1 mg/kg BID followed by vitamin K antagonist. Each treatment was administered for 12 wk. The primary efficacy end point was an improvement in thrombotic burden at day 21 (assessed by quant. compression ultrasonog.; ≥4-point improvement in thrombus score) without recurrent symptomatic venous thromboembolism or venous thromboembolism-related death. The primary safety end point was major bleeding during 12 wk of treatment. Outcomes were adjudicated centrally without knowledge of treatment allocation. The primary efficacy end point was achieved in 53 (53.0%) of 100, 58 (59.2%) of 98, 62 (56.9%) of 109, and 49 (43.8%) of 112 patients receiving rivaroxaban 10, 20, or 30 mg BID or 40 mg once daily, resp., compared with 50 (45.9%) of 109 patients treated with enoxaparin/vitamin K antagonist. There was no significant trend in the dose-response relationship between rivaroxaban BID and the primary efficacy end point (P = 0.67). Major bleeding was observed in 1.7%, 1.7%, 3.3%, and 1.7% of patients receiving rivaroxaban 10, 20, or 30 mg BID or 40 mg once daily, resp. There were no major bleeding events with enoxaparin/vitamin K antagonist. Conclusions: Results of this proof-of-concept and dose-finding study support phase III evaluation of the orally active direct factor Xa inhibitor rivaroxaban, because efficacy and safety were apparent in the treatment of proximal deep-vein thrombosis across a 3-fold range of fixed daily dosing.
CC 1-8 (Pharmacology)
IT Human
Oral drug delivery systems
(oral factor Xa inhibitor rivaroxaban was effective and safe in patient with acute symptomatic deep-vein thrombosis)
IT 366789-02-8, Rivaroxaban
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral factor Xa inhibitor rivaroxaban was effective and safe in patient with acute symptomatic deep-vein thrombosis)
IT 366789-02-8, Rivaroxaban
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral factor Xa inhibitor rivaroxaban was effective and safe in patient

with acute symptomatic deep-vein thrombosis)
RN 366789-02-8 CAPLUS
CN 2-Thiophenecarboxamide, 5-chloro-N-[[(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-5-oxazolidinyl]methyl]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 63 THERE ARE 63 CAPLUS RECORDS THAT CITE THIS RECORD (63 CITINGS)
REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L48 ANSWER 17 OF 17 CAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 2006:759552 CAPLUS Full-text
DOCUMENT NUMBER: 145:195683
TITLE: Prevention and treatment of thromboembolic disorders by administering a direct factor Xa inhibitor
INVENTOR(S): Misselwitz, Frank; Kubitza, Dagmar; Park, Son-Mi; Wehling, Klaus
PATENT ASSIGNEE(S): Bayer Healthcare A.-G., Germany
SOURCE: PCT Int. Appl., 20pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006079474	A1	20060803	WO 2006-EP431	20060119
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
EP 1685841	A1	20060802	EP 2005-1893	20050131
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, BA, HR, IS, YU				
AU 2006208613	A1	20060803	AU 2006-208613	20060119
CA 2596145	A1	20060803	CA 2006-2596145	20060119

EP 1845961	A1	20071024	EP 2006-706291		20060119
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, HR					
JP 2008528527	T	20080731	JP 2007-552555		20060119
BR 2006006760	A2	20090714	BR 2006-6760		20060119
SG 159505	A1	20100330	SG 2010-639		20060119
NZ 556765	A	20101126	NZ 2006-556765		20060119
AR 52565	A1	20070321	AR 2006-100331		20060130
IN 2007DN05660	A	20070817	IN 2007-DN5660		20070723
KR 2007107009	A	20071106	KR 2007-7017201		20070726
MX 2007009100	A	20070913	MX 2007-9100		20070727
ZA 2007006238	A	20081126	ZA 2007-6238		20070727
CN 101111236	A	20080123	CN 2006-80003676		20070731
NO 2007004356	A	20070827	NO 2007-4356		20070827
US 20090004265	A1	20090101	US 2008-883218		20080716
PRIORITY APPLN. INFO.:			EP 2005-1893	A	20050131
			WO 2006-EP431	W	20060119

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

ED Entered STN: 03 Aug 2006

AB The present invention relates to the field of blood coagulation, more specifically it relates to a method of treating a thromboembolic disorder by administering once daily a direct factor Xa inhibitor in oral dosage form to a patient in need thereof, wherein the factor Xa inhibitor has a plasma concentration half life indicative of a bid or tid administration interval, e.g. of 10 h or less.

IPCI A61K0031-00 [I,A]; A61K0031-5377 [I,A]; A61P0007-02 [I,A]; A61P0009-10 [I,A]

CC 63-6 (Pharmaceuticals)

IT Drug delivery systems
(oral; prevention and treatment of thromboembolic disorders by administering direct factor Xa inhibitor)

IT Drug delivery systems
(tablets, immediate release; prevention and treatment of thromboembolic disorders by administering direct factor Xa inhibitor)

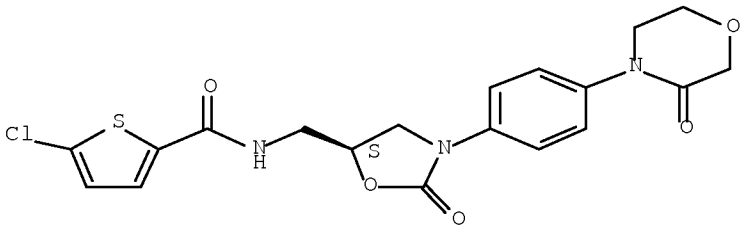
IT 366789-02-8 679809-58-6, Enoxaparin sodium
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prevention and treatment of thromboembolic disorders by administering direct factor Xa inhibitor)

IT 366789-02-8
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prevention and treatment of thromboembolic disorders by administering direct factor Xa inhibitor)

RN 366789-02-8 CAPLUS

CN 2-Thiophenecarboxamide, 5-chloro-N-[[(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-5-oxazolidinyl]methyl]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD

(4 CITINGS)

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

INVENTOR SEARCH

```
=> d que nos l49
L4              STR
L6            32 SEA FILE=REGISTRY FAM FUL L4
L11          229 SEA FILE=CAPLUS SPE=ON  ABB=ON  PLU=ON  L6
L13          189 SEA FILE=CAPLUS SPE=ON  ABB=ON  PLU=ON  L11 (L) (THU OR
                 PAC)/RL
L14         5813 SEA FILE=CAPLUS SPE=ON  ABB=ON  PLU=ON  (RAPID (3A) RELEAS?)/BI

L17       270925 SEA FILE=CAPLUS SPE=ON  ABB=ON  PLU=ON  DRUG DELIVER?/OBI
L19       230417 SEA FILE=CAPLUS SPE=ON  ABB=ON  PLU=ON  (DAILY )/BI
L21        46546 SEA FILE=CAPLUS SPE=ON  ABB=ON  PLU=ON  ORAL/OBI (L) L17
L22        31769 SEA FILE=CAPLUS SPE=ON  ABB=ON  PLU=ON  TABLET/OBI (L) L17
L27      1109302 SEA FILE=CAPLUS SPE=ON  ABB=ON  PLU=ON  DOS####/BI
L29           52 SEA FILE=CAPLUS SPE=ON  ABB=ON  PLU=ON  MISSELWITZ F?/AU
L30           42 SEA FILE=CAPLUS SPE=ON  ABB=ON  PLU=ON  KUBITZA D?/AU
L31        39724 SEA FILE=CAPLUS SPE=ON  ABB=ON  PLU=ON  PARK S?/AU
L32           32 SEA FILE=CAPLUS SPE=ON  ABB=ON  PLU=ON  WEHLING K?/AU
L33        39843 SEA FILE=CAPLUS SPE=ON  ABB=ON  PLU=ON  (L29 OR L30 OR L31 OR
                 L32)
L34           34 SEA FILE=CAPLUS SPE=ON  ABB=ON  PLU=ON  L33 AND L11
L35           20 SEA FILE=CAPLUS SPE=ON  ABB=ON  PLU=ON  L34 AND L19
L37           13 SEA FILE=CAPLUS SPE=ON  ABB=ON  PLU=ON  L34 AND ((L21 OR L22))

L38           23 SEA FILE=CAPLUS SPE=ON  ABB=ON  PLU=ON  L37 OR L35
L41            9 SEA FILE=CAPLUS SPE=ON  ABB=ON  PLU=ON  L14 AND L33
L42            2 SEA FILE=CAPLUS SPE=ON  ABB=ON  PLU=ON  L41 AND ((L21 OR L22))

L43           25 SEA FILE=CAPLUS SPE=ON  ABB=ON  PLU=ON  L42 OR L38
L46           68 SEA FILE=CAPLUS SPE=ON  ABB=ON  PLU=ON  L13 AND ((L21 OR L22))

L47           35 SEA FILE=CAPLUS SPE=ON  ABB=ON  PLU=ON  L46 AND L27
L48           17 SEA FILE=CAPLUS SPE=ON  ABB=ON  PLU=ON  L47 AND L19
L49           16 SEA FILE=CAPLUS SPE=ON  ABB=ON  PLU=ON  L43 NOT L48


=> d ibib hitind l49 1-16

L49  ANSWER 1 OF 16  CAPLUS  COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER:         2009:814369  CAPLUS  Full-text
DOCUMENT NUMBER:          152:206536
TITLE:                    Rivaroxaban versus placebo in patients with acute
                          coronary syndromes (ATLAS ACS-TIMI 46): a randomised,
                          double-blind, phase II trial
AUTHOR(S):                Mega, J. L.; Braunwald, E.; Mohanavelu, S.; Burton,
                          P.; Poulter, R.; Misselwitz, F.; Hricak, V.;
                          Barnathan, E. S.; Bordes, P.; Witkowski, A.; Markov,
                          V.; Oppenheimer, L.; Gibson, C. M.
CORPORATE SOURCE:         TIMI Study Group, Boston, MA, USA
SOURCE:                   Lancet (2009), 374(9683), 29-38
                          CODEN: LANCAO; ISSN: 0140-6736
PUBLISHER:                Elsevier Ltd.
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
CC   1-8 (Pharmacology)
IT   50-78-2, Aspirin   366789-02-8, Rivaroxaban
     RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
     (Biological study); USES (Uses)
        (rivaroxaban vs. placebo in patients with acute coronary syndrome)
```

OS.CITING REF COUNT: 39 THERE ARE 39 CAPLUS RECORDS THAT CITE THIS RECORD (39 CITINGS)
REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 2 OF 16 CAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 2009:601060 CAPLUS Full-text
DOCUMENT NUMBER: 151:417821
TITLE: Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial
AUTHOR(S): Turpie, Alexander G. G.; Lassen, Michael R.; Davidson, Bruce L.; Bauer, Kenneth A.; Gent, Michael; Kwong, Louis M.; Cushner, Fred D.; Lotke, Paul A.; Berkowitz, Scott D.; Bandel, Tiemo J.; Benson, Alice; Misselwitz, Frank; Fisher, William D.
CORPORATE SOURCE: McMaster University, Hamilton, Can.
SOURCE: Lancet (2009), 373(9676), 1673-1680
CODEN: LANCAO; ISSN: 0140-6736
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
CC 1-8 (Pharmacology)
IT Anticoagulants
Arthroplasty
Human
Oral drug delivery systems
Pulmonary embolism
(rivaroxaban vs. enoxaparin for thromboprophylaxis after total knee arthroplasty)
IT 366789-02-8, Rivaroxaban 679809-58-6, Enoxaparin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(rivaroxaban vs. enoxaparin for thromboprophylaxis after total knee arthroplasty)
OS.CITING REF COUNT: 59 THERE ARE 59 CAPLUS RECORDS THAT CITE THIS RECORD (59 CITINGS)
REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 3 OF 16 CAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 2008:1465523 CAPLUS Full-text
DOCUMENT NUMBER: 150:463265
TITLE: Dose-escalation study of the pharmacokinetics and pharmacodynamics of rivaroxaban in healthy elderly subjects
AUTHOR(S): Kubitza, Dagmar; Becka, Michael; Roth, Angelika; Mueck, Wolfgang
CORPORATE SOURCE: Clinical Pharmacology, Bayer HealthCare AG, Wuppertal, D-42096, Germany
SOURCE: Current Medical Research and Opinion (2008), 24(10), 2757-2765
CODEN: CMROCX; ISSN: 0300-7995
PUBLISHER: Informa Healthcare
DOCUMENT TYPE: Journal
LANGUAGE: English
CC 1-2 (Pharmacology)
IT Anticoagulants
Human
Oral drug delivery systems

(novel oral direct factor Xa inhibitor rivaroxaban was safe and well tolerated with predictable pharmacokinetic, pharmacodynamic profiles in healthy elderly human)

IT 366789-02-8, Rivaroxaban
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(novel oral direct factor Xa inhibitor rivaroxaban was safe and well tolerated with predictable pharmacokinetic, pharmacodynamic profiles in healthy elderly human)

OS.CITING REF COUNT: 15 THERE ARE 15 CAPLUS RECORDS THAT CITE THIS RECORD (15 CITINGS)
REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 4 OF 16 CAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 2008:1204277 CAPLUS Full-text
DOCUMENT NUMBER: 149:462639
TITLE: Population pharmacokinetics and pharmacodynamics of once- and twice-daily rivaroxaban for the prevention of venous thromboembolism in patients undergoing total hip replacement
AUTHOR(S): Mueck, Wolfgang; Borris, Lars C.; Dahl, Ola E.; Haas, Sylvia; Huisman, Menno V.; Kakkar, Ajay K.; Kaelebo, Peter; Muelhofer, Eva; Misselwitz, Frank; Eriksson, Bengt I.
CORPORATE SOURCE: Bayer HealthCare AG, Wuppertal, Germany
SOURCE: Thrombosis and Haemostasis (2008), 100(3), 453-461
CODEN: THHADQ; ISSN: 0340-6245
PUBLISHER: Schattauer GmbH
DOCUMENT TYPE: Journal
LANGUAGE: English
CC 1-8 (Pharmacology)
IT 366789-02-8, Rivaroxaban
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(rivaroxaban pharmacokinetics and pharmacodynamics in prevention of venous thromboembolism under hip replacement)

OS.CITING REF COUNT: 26 THERE ARE 26 CAPLUS RECORDS THAT CITE THIS RECORD (26 CITINGS)
REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 5 OF 16 CAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 2008:1148862 CAPLUS Full-text
DOCUMENT NUMBER: 149:347175
TITLE: A dose-ranging study evaluating once-daily oral administration of the factor Xa inhibitor rivaroxaban in the treatment of patients with acute symptomatic deep vein thrombosis: the Einstein-DVT Dose-Ranging Study
AUTHOR(S): Buller, Harry R.; Lensing, Anthonie W. A.; Prins, Martin H.; Agnelli, Giancarlo; Cohen, Alexander; Gallus, Alexander S.; Misselwitz, Frank; Raskob, Gary; Schellong, Sebastian; Segers, Annelise
CORPORATE SOURCE: The Einstein-DVT Dose-Ranging Study investigators, Department of Vascular Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, Neth.
SOURCE: Blood (2008), 112(6), 2242-2247
CODEN: BLOOAW; ISSN: 0006-4971
PUBLISHER: American Society of Hematology

DOCUMENT TYPE: Journal
LANGUAGE: English
CC 1-8 (Pharmacology)
IT 366789-02-8, Rivaroxaban
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(dose-ranging study evaluating rivaroxaban in treatment of patients with acute symptomatic deep vein thrombosis)
OS.CITING REF COUNT: 46 THERE ARE 46 CAPLUS RECORDS THAT CITE THIS RECORD (46 CITINGS)
REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 6 OF 16 CAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 2008:792353 CAPLUS Full-text
DOCUMENT NUMBER: 149:44820
TITLE: Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty
AUTHOR(S): Lassen, Michael R.; Ageno, Walter; Borris, Lars C.; Lieberman, Jay R.; Rosencher, Nadia; Bandel, Tiemo J.; Misselwitz, Frank; Turpie, Alexander G. G.
CORPORATE SOURCE: Nordsjaellands Hospital, Hoersholm, Den.
SOURCE: New England Journal of Medicine (2008), 358(26), 2776-2786
CODEN: NEJMAG; ISSN: 0028-4793
PUBLISHER: Massachusetts Medical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
CC 1-8 (Pharmacology)
IT 366789-02-8, Rivaroxaban 679809-58-6, Clexane
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(rivaroxaban vs. enoxaparin for thromboprophylaxis after total knee arthroplasty)
OS.CITING REF COUNT: 108 THERE ARE 108 CAPLUS RECORDS THAT CITE THIS RECORD (108 CITINGS)
REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 7 OF 16 CAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 2008:115184 CAPLUS Full-text
DOCUMENT NUMBER: 148:410706
TITLE: Method for manufacturing controlled-release oral bilayer tablet containing loxoprofen
INVENTOR(S): Ahn, Gi Yeong; Kil, Yeong Sik; Jung, Sang Yeong; Ha, Dae Cheol; Ahn, Geon Seok; Shin, Hyeon Mo; Park, Sang Man; Park, Hui Chan; Seo, Yeong Sam; Song, Hui Yong
PATENT ASSIGNEE(S): Korea United Pharmaceutical, Inc., S. Korea
SOURCE: Repub. Korean Kongkae Taeho Kongbo, 10pp.
CODEN: KRXXA7
DOCUMENT TYPE: Patent
LANGUAGE: Korean
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
KR 2008002103	A	20080104	KR 2006-60717	20060630
KR 794169	B1	20080111		

PRIORITY APPLN. INFO.: KR 2006-60717 20060630
IPCI A61K0009-22 [I,A]; A61K0031-19 [I,A]; A61K0031-185 [I,C*]
CC 63-6 (Pharmaceuticals)
IT Controlled-release drug delivery systems
(tablets; method for manufacturing controlled-release oral bilayer tablet containing loxoprofen)

L49 ANSWER 8 OF 16 CAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 2007:1358959 CAPLUS Full-text
DOCUMENT NUMBER: 148:182387
TITLE: Effects of the oral, direct factor Xa inhibitor rivaroxaban on platelet-induced thrombin generation and prothrombinase activity
AUTHOR(S): Graff, Jochen; von Hentig, Nils; Misselwitz, Frank; Kubitza, Dagmar; Becka, Michael; Breddin, Hans-Klaus; Harder, Sebastian
CORPORATE SOURCE: Pharmazentrum Frankfurt/ZAFES, Institute of Clinical Pharmacology, University Hospital, Frankfurt am Main, Germany
SOURCE: Journal of Clinical Pharmacology (2007), 47(11), 1398-1407
CODEN: JCPCBR; ISSN: 0091-2700
PUBLISHER: Sage Publications
DOCUMENT TYPE: Journal
LANGUAGE: English
CC 1-2 (Pharmacology)
IT Blood platelet
Human
Oral drug delivery systems
(oral, direct factor Xa inhibitor rivaroxaban inhibited platelet-induced thrombin generation and prothrombinase activity in human)
IT 366789-02-8, BAY 59-7939
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral, direct factor Xa inhibitor rivaroxaban inhibited platelet-induced thrombin generation and prothrombinase activity in human)
OS.CITING REF COUNT: 26 THERE ARE 26 CAPLUS RECORDS THAT CITE THIS RECORD (26 CITINGS)
REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 9 OF 16 CAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 2007:1191254 CAPLUS Full-text
DOCUMENT NUMBER: 147:455549
TITLE: Oral extended-release compositions containing tolterodine tartrate
INVENTOR(S): Shin, Hyun Mo; Gil, Young Sig; Jung, Won Tae; Jeong, Sang Young; Ahn, Ki Young; Park, Sang Man; Ha, Dae Chul; Park, Hee Chan; Kim, Hye Kyung
PATENT ASSIGNEE(S): Korea United Pharm. Inc., S. Korea
SOURCE: Repub. Korea, No pp. given
CODEN: KRXXFC
DOCUMENT TYPE: Patent
LANGUAGE: Korean
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

KR 714058	B1	20070502	KR 2006-11048	20060206
PRIORITY APPLN. INFO.:			KR 2006-11048	20060206

IPCI A61K0031-137 [I,A]; A61K0047-48 [I,A]
CC 63-6 (Pharmaceuticals)
IT Controlled-release drug delivery systems
Human
Oral drug delivery systems
(oral extended-release compns. containing tolterodine tartrate)

L49 ANSWER 10 OF 16 CAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 2007:956846 CAPLUS Full-text
DOCUMENT NUMBER: 147:419675
TITLE: Dose-escalation study of rivaroxaban (BAY 59-7939) - an oral, direct Factor Xa inhibitor - for the prevention of venous thromboembolism in patients undergoing total hip replacement
AUTHOR(S): Eriksson, Bengt I.; Borris, Lars C.; Dahl, Ola E.; Haas, Sylvia; Huisman, Menno V.; Kakkar, Ajay K.; Misselwitz, Frank; Muehlhofer, Eva; Kaelebo, Peter
CORPORATE SOURCE: Department of Orthopaedics, Sahlgrenska University Hospital/Oestra, Goteborg, SE-41685, Swed.
SOURCE: Thrombosis Research (2007), 120(5), 685-693
CODEN: THBRAA; ISSN: 0049-3848
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
CC 1-8 (Pharmacology)
IT 366789-02-8, Rivaroxaban
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral factor Xa inhibitor rivaroxaban for prevention of venous thromboembolism in patients undergoing total hip replacement)
OS.CITING REF COUNT: 31 THERE ARE 31 CAPLUS RECORDS THAT CITE THIS RECORD (31 CITINGS)
REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 11 OF 16 CAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 2007:936427 CAPLUS Full-text
DOCUMENT NUMBER: 147:377265
TITLE: Preclinical and clinical characteristics of rivaroxaban: a novel, oral, direct factor Xa inhibitor
AUTHOR(S): Laux, Volker; Perzborn, Elisabeth; Kubitza, Dagmar; Misselwitz, Frank
CORPORATE SOURCE: Cardiovascular Research, Bayer Schering Pharma, Wuppertal, Germany
SOURCE: Seminars in Thrombosis and Hemostasis (2007), 33(5), 515-523
CODEN: STHMBV; ISSN: 0094-6176
PUBLISHER: Thieme Medical Publishers, Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
CC 1-0 (Pharmacology)
IT 366789-02-8, Rivaroxaban 679809-58-6, Enoxaparin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral factor Xa inhibitor rivaroxaban may be safe, tolerated and similarly effective to enoxaparin in patient with venous

thromboembolism after major orthopedic surgery)
OS.CITING REF COUNT: 13 THERE ARE 13 CAPLUS RECORDS THAT CITE THIS RECORD (14 CITINGS)
REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 12 OF 16 CAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 2007:681790 CAPLUS Full-text
DOCUMENT NUMBER: 147:45753
TITLE: Rivaroxaban for thromboprophylaxis after orthopaedic surgery: pooled analysis of two studies
AUTHOR(S): Fisher, William D.; Eriksson, Bengt I.; Bauer, Kenneth A.; Borris, Lars; Dahl, Ola E.; Gent, Michael; Haas, Sylvia; Homering, Martin; Huisman, Menno V.; Kakkar, Ajay K.; Kalebo, Peter; Kwong, Louis M.; Misselwitz, Frank; Turpie, Alexander G. G.
CORPORATE SOURCE: McGill University Health Centre, Montreal, Can.
SOURCE: Thrombosis and Haemostasis (2007), 97(6), 931-937
CODEN: THHADQ; ISSN: 0340-6245
PUBLISHER: Schattauer GmbH
DOCUMENT TYPE: Journal
LANGUAGE: English
CC 1-8 (Pharmacology)
IT 366789-02-8, Rivaroxaban 679809-58-6, Enoxaparin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(rivaroxaban for thromboprophylaxis after orthopedic surgery)
OS.CITING REF COUNT: 31 THERE ARE 31 CAPLUS RECORDS THAT CITE THIS RECORD (32 CITINGS)
REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 13 OF 16 CAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 2006:1219907 CAPLUS Full-text
DOCUMENT NUMBER: 146:266252
TITLE: A once-daily, oral, direct factor Xa inhibitor, rivaroxaban (BAY 59-7939), for thromboprophylaxis after total hip replacement
AUTHOR(S): Eriksson, Bengt I.; Borris, Lars C.; Dahl, Ola E.; Haas, Sylvia; Huisman, Menno V.; Kakkar, Ajay K.; Muehlhofer, Eva; Dierig, Christoph; Misselwitz, Frank; Kaelebo, Peter
CORPORATE SOURCE: ODIXa-HIP Study Investigators, Department of Orthopaedics, Sahlgrenska University Hospital/Oestra, Goeteborg, Swed.
SOURCE: Circulation (2006), 114(22), 2374-2381
CODEN: CIRCAZ; ISSN: 0009-7322
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
CC 1-8 (Pharmacology)
IT Anticoagulants
Human
Prophylaxis
Surgery
(once-daily oral, direct factor Xa inhibitor rivaroxaban showed efficacy and safety similar to Clexane for prevention of venous thromboembolism in patient who underwent elective total hip replacement surgery)
IT Embolism

Thrombosis
(thromboembolism; once-daily oral, direct factor Xa inhibitor rivaroxaban showed efficacy and safety similar to Clexane for prevention of venous thromboembolism in patient who underwent elective total hip replacement surgery)
IT 366789-02-8, Rivaroxaban
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(once-daily oral, direct factor Xa inhibitor rivaroxaban showed efficacy and safety similar to Clexane for prevention of venous thromboembolism in patient who underwent elective total hip replacement surgery)
IT 9002-05-5, Factor Xa
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(once-daily oral, direct factor Xa inhibitor rivaroxaban showed efficacy and safety similar to Clexane for prevention of venous thromboembolism in patient who underwent elective total hip replacement surgery)
IT 679809-58-6, Clexane
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(once-daily oral, direct factor Xa inhibitor rivaroxaban showed efficacy and safety similar to Clexane for prevention of venous thromboembolism in patient who underwent elective total hip replacement surgery)
OS.CITING REF COUNT: 76 THERE ARE 76 CAPLUS RECORDS THAT CITE THIS RECORD (77 CITINGS)
REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 14 OF 16 CAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 2006:479517 CAPLUS Full-text
DOCUMENT NUMBER: 145:328032
TITLE: Effects of food, an antacid, and the H2 anatagonist ranitidine on the absorption of BAY 59-7939 (Rivaroxaban), an oral, direct factor Xa inhibitor, in healthy subjects
AUTHOR(S): Kubitza, Dagmar; Becka, Michael; Zuehlsdorf, Michael; Mueck, Wolfgang
CORPORATE SOURCE: Bayer HealthCare AG, Wuppertal, Germany
SOURCE: Journal of Clinical Pharmacology (2006), 46(5), 549-558
CODEN: JCPCBR; ISSN: 0091-2700
PUBLISHER: Sage Publications
DOCUMENT TYPE: Journal
LANGUAGE: English
CC 1-8 (Pharmacology)
IT 366789-02-8, Rivaroxaban
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmacokinetic and pharmacodynamic properties of rivaroxaban were moderately altered by food, resulting in delayed absorption and in increased peak concentration and prolongation of PT but were unaffected by ranitidine or antacid in human)
OS.CITING REF COUNT: 42 THERE ARE 42 CAPLUS RECORDS THAT CITE THIS RECORD (42 CITINGS)
REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 15 OF 16 CAPLUS COPYRIGHT 2011 ACS on STN

ACCESSION NUMBER: 2006:92133 CAPLUS Full-text
DOCUMENT NUMBER: 145:20765
TITLE: Oral, direct factor Xa inhibition with BAY 59-7939 for the prevention of venous thromboembolism after total hip replacement
AUTHOR(S): Eriksson, B. I.; Borris, L.; Dahl, O. E.; Haas, S.; Huisman, M. V.; Kakkar, A. K.; Misselwitz, F. ; Kaelebo, P.
CORPORATE SOURCE: The ODIXA-HIP Study Investigators, Sahlgrenska University Hospital/Oestra, Goeteborg, SW-416, Swed.
SOURCE: Journal of Thrombosis and Haemostasis (2006), 4(1), 121-128
CODEN: JTHOA5; ISSN: 1538-7933
PUBLISHER: Blackwell Publishing, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
CC 1-8 (Pharmacology)
IT 366789-02-8, BAY 59-7939
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral, direct FXa inhibitor BAY 59-7939 at 2.5-10 mg b.i.d. was effective and compared favorably with enoxaparin for prevention of venous thromboembolism in European and Israeli patients undergoing elective total hip replacement)
OS.CITING REF COUNT: 104 THERE ARE 104 CAPLUS RECORDS THAT CITE THIS RECORD (105 CITINGS)
REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 16 OF 16 CAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 2005:1267623 CAPLUS Full-text
DOCUMENT NUMBER: 144:266923
TITLE: BAY 59-7939: An oral, direct Factor Xa inhibitor for the prevention of venous thromboembolism in patients after total knee replacement. A phase II dose-ranging study
AUTHOR(S): Turpie, A. G. G.; Fisher, W. D.; Bauer, K. A.; Kwong, L. M.; Irwin, M. W.; Kalebo, P.; Misselwitz, F.; Gent, M.
CORPORATE SOURCE: The ODIXa-Knee Study Group, HHS-General Hospital, Hamilton, Can.
SOURCE: Journal of Thrombosis and Haemostasis (2005), 3(11), 2479-2486
CODEN: JTHOA5; ISSN: 1538-7933
PUBLISHER: Blackwell Publishing, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
CC 1-8 (Pharmacology)
Section cross-reference(s): 63
IT Drug delivery systems
(oral; postoperative oral administration of BAY 59-7939 showed potential efficacy, acceptable safety profile similar to enoxaparin for prevention of venous thromboembolism in patient undergoing elective total knee replacement)
IT 366789-02-8 679809-58-6, Enoxaparin sodium
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(postoperative oral administration of BAY 59-7939 showed potential efficacy, acceptable safety profile similar to enoxaparin for prevention of venous thromboembolism in patient undergoing elective

```
        total knee replacement)
OS.CITING REF COUNT:     105   THERE ARE 105 CAPLUS RECORDS THAT CITE THIS
                               RECORD (105 CITINGS)
REFERENCE COUNT:          18   THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS
                               RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
```

PTO/SB/08b (04-09)
Approved for use through 05/31/2009. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 4

Complete if Known	
Application Number	11/883,218-Conf. #9960
Filing Date	July 16, 2008
First Named Inventor	Frank Misselwitz
Art Unit	1615
Examiner Name	Not Yet Assigned
Attorney Docket Number	11987-00042-US

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

NON PATENT LITERATURE DOCUMENTS

Examiner Initials	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
/J.K./	CA	WHITE, R.H., "The Epidemiology of Venous Thromboembolism", Circulation, (2003), Vol. 107, (Suppl. 1), pp. I-4 - I-8.	
/J.K./	CB	FEIGN, V.L., et al., "Stroke Epidemiology: A Review of Population-Based Studies of Incidence, Prevalence, and Case-Fatality in the Late 20th Century", The Lancet Neurology, (2003), Vol. 2, pp. 43-53.	
/J.K./	CC	FANG, J., et al., "Dissociation of Hospitalization and Mortality Trends for Myocardial Infarction in the United States from 1988 to 1997", The American Journal of Medicine, (2002), Vol. 113, pp. 208-214.	
/J.K./	CD	RAGHAVEN, S.A.V., et al., "Recent Advances in the Status and Targets of Antithrombotic Agents", Drugs of the Future, (2002), Vo.. 27, No. 7, pp. 669-683.	
/J.K./	CE	WIELAND, H.A., et al., "Approaches in Anticoagulation: Rationales for Target Positioning", Current Opinion in Investigational Drugs, (2003), Vol. 4, No. 3. pp. 264-271.	
/J.K./	CF	RIES, U.J., et al., "Serine Proteases as Targets for Antithrombotic Therapy", Drugs of the Future, (2003), Vol. 28, No. 4, pp. 355-370.	
/J.K./	CG	LINKINS, L-A., et al., "New Anticoagulant Therapy", Annu. Rev. Med., (2005), Vol. 56, pp. 63-77.	
/J.K./	CH	GOODMAN AND GILLMAN, "The Pharmacological Basis of Therapeutics", 7th Ed., MacMillian Publishing Co., NY, (1985), pp. 27-28.	
/J.K./	CI	ROWLAND, M., et al., "Multiple-Dose Regimens", Clinical Pharmacokinetics, Concepts and Applications, 3rd Ed, Lea & Febiger, Williams & Wilkins, Media, PA (1995), pp. 83-105.	
/J.K./	CJ	BIRKETT, D.J., "Why is Half-Life Important", Pharmacokinetics Made Easy, McGraw-Hill Education, (2000), pp. 20-21.	

Examiner Signature	/Jody Karol/	Date Considered	03/10/2011

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1]Applicant's unique citation designation number (optional). [2]Applicant is to place a check mark here if English language Translation is attached.

PTO/SB/08b (04-09)
Approved for use through 05/31/2009. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 4

Complete if Known	
Application Number	11/883,218-Conf. #9960
Filing Date	July 16, 2008
First Named Inventor	Frank Misselwitz
Art Unit	1615
Examiner Name	Not Yet Assigned
Attorney Docket Number	11987-00042-US

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
/J.K./	CK	ROEHRIG, S., et al., "Discovery of the Novel Antithrombotic Agent Bay 59-7939, an Orally Active, Direct Factor XA Inhibitor", 228th ACS National Meeting, (2004), MEDI-156.	
/J.K./	CL	GEERTS, W.H., et al., "Prevention of Venous Thromboembolism", Chest, (2001), Vol. 119, pp. 132S-175S.	
/J.K./	CM	TAKEHANA, S., et al., "Antithrombotic Effect of AX1826, A Novel Inhibitor of Factor Xa, in the Rat Thrombosis Models", Japanese Journal of Pharmacology, (2000), 82 (Suppl. 1), 213P.	
/J.K./	CN	JUST, M., et al., "A Comparison of a Specific Factor Xa Inhibitor (HMR-2906) and Recombinant Hirudin in a Dog Coronary Artery Thrombosis Model", XVIIth Congress of the International Society for Thrombosis and Haemostasis, Washington, D.C., (1999).	
/J.K./	CO	CHU, V., et al., "Pharmacological Characterization of a Novel Factor Xa Inhibitor, FXV673", Thrombosis Research, (2001), Vol. 103, pp. 309-324.	
/J.K./	CP	GUERTIN, K.R., et al., "Optimization of the β-Aminoester Class of Factor Xa Inhibitors. Part 2: Identification of FXV673 as a Potent and Selective Inhibitor with Excellent In Vivo Anticoagulant Activity", Bioorganic & Medicinal Chemistry Letters, (2002), Vol. 12, pp. 1671-1674.	
/J.K./	CQ	RIES, U.J., et al., "Heterocyclic Coagulation Inhibitors: Design and Synthesis of Dual Direct Thrombin and Factor Xa Inhibitors", American Chemical Society - 226th National Meeting, (2003).	
/J.K./	CR	PRUITT, JAMES R., et al., "Discovery of 1-(2-Aminomethylphenyl)-3-trifluoromethyl-N- [3-fluoro-2'-(aminosulfonyl)[1,1'-biphenyl)]-4-yl]-1 *H*-pyrazole-5-carboxyamide (DPC602), a Potent, Selective, and Orally Bioavailable Factor Xa Inhibitor", J. Med. Chem., (2003), Vol. 46, No. 25, pp. 5298-5315.	
/J.K./	CS	NAGAHARA, T., et al., "Dibasic (Amidinoaryl)propanoic Acid Derivatives as Novel Blood Coagulation Factor Xa Inhibitors", J. Med. Chem., (1994), Vol. 37, No. 8, pp. 1200-1207.	

Examiner Signature	/Jody Karol/	Date Considered	03/10/2011

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1]Applicant's unique citation designation number (optional). [2]Applicant is to place a check mark here if English language Translation is attached.

PTO/SB/08b (04-09)
Approved for use through 05/31/2009. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 3 of 4

Complete if Known	
Application Number	11/883,218-Conf. #9960
Filing Date	July 16, 2008
First Named Inventor	Frank Misselwitz
Art Unit	1615
Examiner Name	Not Yet Assigned
Attorney Docket Number	11987-00042-US

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s) , volume-issue number(s), publisher, city and/or country where published.	T[2]
/J.K./	CT	MORISHIMA, Y., et al., "*In Vitro* Characteristics, Anticoagulant Effects and *In Vivo* Antithrombotic Efficacy of a Novel, Potent and Orally Active Direct Factor Xa Inhibitor, DU-176b", Blood, (2004), (Abst 1862).	
/J.K./	CU	FUKUDA, T., et al., "Antithrombotic Properties of DU-176b, a Novel, Potent and Orally Active Direct Factor Xa Inhibitor in Rat Models of Arterial and Venous Thrombosis: Comparison with Fondaparinux, an Antithrombin Dependent Factor Xa Inhibitor", Blood, (2004), (Abst 1852).	
/J.K./	CV	FURUGOHRI, T., et al, "Antithrombotic and Hemorrhagic Effects of DU-176b, a Novel, Potent and Orally Active Direct Factor Xa Inhibitor: A Wider Safety Margin Compared to Heparins and Warfarin", Blood, (2004), (Abst. 1851).	
/J.K./	CW	Proteinase 2004: Strategies for New Medicines, 4th SCI-RSC Symposium, Proteinase Inhibitor Design, (2004).	
/J.K./	CX	KOIZUMI, T. et al., "Effect of KFA-1982, a New Orally Active Factor Xa Inhibitor, in a Rabbit Venous Thrombosis Model", J. of Thrombosis and Haemostasis, Vol. 1, Suppl. 1, (2003), P2022. (abstract)	
/J.K./	CY	NISHIDA, H., et al., "Synthesis and Evaluation of 1-Arylsulfonyl-3-piperazinone Derivatives as Factor Xa Inhibitors[1,2] III. Effect of Ring Opening of Piperazinone Moiety on Inhibition", Chem. Pharm. Bull, (2004), Vol. 52, No. 4. pp. 459-462.	
/J.K./	CZ	NISHIDA, H., et al., "Synthesis and Evaluation of 1-Arylsulfonyl-3-piperazinone Derivatives as Factor Xa Inhibitors [1-3] IV. A Series of New Derivatives Containing a Spiro [5*H*-oxazolo[3,2-*a*]pyrazine-2(3*H*),4' -piperidin]-5-one Skeleton", Chem. Pharm. Bull., (2004), Vol. 52, No. 4, pp. 406-412.	
/J.K./	CA1	NISHIDA, H., et al., "Synthesis and Evaluation of 1-Arylsulfonyl-3-piperazinone Derivatives as a Factor Xa Inhibitor[1,2] II. Substituent Effect on Biological Activities", Chem. Pharm. Bull., (2002), Vol. 50, No. 9, pp. 1187-1194.	
/J.K./	CB1	NISHIDA, H., et al., "Synthesis and Evaluation of 1-Arylsulfonyl-3-piperazinone Derivatives as Factor Xa Inhibitor", Chem. Pharm. Bull. Vol. 49, No. 10, (2001), pp. 1237-1244.	
/J.K./	CC1	YOUNG, S. C., "Factor Xa Inhibitor LY517717; A Novel and Effective Oral Anticoagulant", Medicinal Chemistry-12th RSC-SCI Symposium, 7-10 September 2003, Cambridge, UK;	
/J.K./	CD1	M. Wiley, et al., 228th ACS National Meeting, Philadelphia, August 22-26, 2004, MEDI-252 & 254.	
/J.K./	CE1	NISHIDA, H. et al., "Design Synthesis and Biological Activities of New Potent Factor Xa Inhibitor," 228th ACS National Meeting, Philadelphia, August 22-26, 2004, Slides from MED1-251.	

Examiner Signature	/Jody Karol/	Date Considered	03/10/2011

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1]Applicant's unique citation designation number (optional). [2]Applicant is to place a check mark here if English language Translation is attached.

PTO/SB/08b (04-09)
Approved for use through 05/31/2009. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 4 of 4

Complete if Known	
Application Number	11/883,218-Conf. #9960
Filing Date	July 16, 2008
First Named Inventor	Frank Misselwitz
Art Unit	1615
Examiner Name	Not Yet Assigned
Attorney Docket Number	11987-00042-US

NON PATENT LITERATURE DOCUMENTS

Examiner Initials	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
/J.K./	CF1	Research and Development Pipeline, Yamanouchi Pharmaceutical Co. Ltd., Company World Wide Web site, "Yamanouchi and Fujisawa Enter Into a Basic Agreement to Merge on April 1, 2005", (2004), 7 pages.	
/J.K./	CG1	NAZARÉ, M., et al., "Novel Factor Xa Inhibitors Based on a 2-Carboxyindole Scaffold: SAR of P4 Substituents in Combination With a Neutral P1 Ligand", Bioorganic & Medicinal Chemistry Letters, Vol. 14, (2004), pp. 4197-4201.	
/J.K./	CH1	NAZARÉ, M., "Novel Factor Xa Inhibitors Based on a Benzoic Acid Scaffold and Incorporating a Neutral P1 Ligand", Bioorganic & Medicinal Chemistry Letters, Vol. 14, (2004), pp. 2801-2805.	
/J.K./	CI1	CHOI-SLEDESKI, Y. M., et al., "Discovery of an Orally Efficacious Inhibitor of Coagulation Factor Xa Which Incorporates a Neutral P Ligand", Journal of Medicinal Chemistry, Vol. 46, No. 5, (2003), pp. 681-684.	
/J.K./	CJ1	MAIGNAN, S., et al., "Molecular Structures of Human Factor Xa Complexed with Ketopiperazine Inhibitors: Preference for a Neutral Group in the S1 Pocket", Journal of Medicinal Chemistry, Vol. 46, No. 5, (2003), pp. 685-690.	
/J.K./	CK1	ADLER, M., et al., "Crystal Structures of Two Potent Nonamidine Inhibitors Bound to Factor Xa", Biochemistry, Vol. 41, No. 52, (2002), pp. 15514-15523.	
/J.K./	CL1	CHOU, Y.-L., et al., "Structure-Activity Relationships of Substituted Benzothiophene-Anthranilamide Factor Xa Inhibitors", Bioorganic & Medicinal Chemistry Letters, Vol. 13, (2003), pp. 507-511.	
/J.K./	CM1	QUAN, M. L., et al., "Discovery of 1-(3'-Aminobenzisoxazol-5'-yl)-3-Trifluoromethyl-*N*-[2-Fluoro-4-[(2'-Dimethylaminomethyl)Imidazol-1-yl]Phenyl]-1*H*-Pyrazole-5-Carboxyamide Hydrochloride (Razaxaban), a Highly Potent, Selective, and Orally Bioavailable Factor Xa Inhibitor", Journal of Medicinal Chemistry, Vol. 48, No. 6, (2005), pp. 1729-1744.	
/J.K./	CN1	PINTO, D. J.P., et al., "Discovery of 1-[3-(Aminomethyl)Phenyl]-*N*-[3-Fluoro-2'-(Methylsulfonyl)-[1,1'-Biphenyl]-4-yl]-3-(Trifluoromethyl)[1*H*-Pyrazole-5-Carboxamide (DPC423), a Highly Potent, Selective, and Orally Bioavailable Inhibitor of Blood Coagulation Factor Xa", Journal of Medicinal Chemistry, Vol. 44, No. 4, (2001), pp. 566-578.	
/J.K./	CO1	HAGINOYA, N., et al., "Synthesis and Conformational Analysis of a Non-Amidine Factor Xa Inhibitor That Incorporates 5-Methyl-4,5,6,7-Tetrahydrothiazolo[5,4-*c*]Pyridine as S4 Binding Element", Journal of Medicinal Chemistry, Vol. 47, No. 21, (2004), pp. 5167-5182.	
/J.K./	CP1	MEDERSKI, W., et al., "Halothiophene Benzimidazoles as P1 Surrogates of Inhibitors of Blood Coagulation Factor Xa", Bioorganic & Medicinal Chemistry Letters, Vol. 14, (2004), pp. 3763-3769.	
/J.K./	CQ1	ZHANG, P., et al., "Design, Synthesis, and SAR of Anthranilamide-Based Factor Xa Inhibitors Incorporating Substituted Biphenyl P4 Motifs", Bioorganic & Medicinal Chemistry Letters, Vol. 14, (2004), pp. 983-987.	
/J.K./	CR1	ZHANG, P., "Design, Synthesis, and SAR of Anthranilamide-based Factor Xa Inhibitors with Improved Functional Activity", Bioorganic & Medicinal Chemistry Letters, Vol.14, (2004), pp. 989-993.	
/J.K./	CS1	WILLARDSEN, J. A., et al., "Design, Synthesis, and Biological Activity of Potent and Selective Inhibitors of Blood Coagulation Factor Xa", Journal of Medicinal Chemistry, Vol. 47, No. 16, (2004), pp. 4089-4099.	

Examiner Signature	/Jody Karol/	Date Considered	03/10/2011

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1]Applicant's unique citation designation number (optional). [2]Applicant is to place a check mark here if English language Translation is attached.

685375_1

Form PTO-1449 (Modified)	U.S. Department of Commerce Patent and Trademark Office	Serial No. Not assigned	Group Art Unit Not known	Filing Date Herewith	Atty. Docket No. BHC 05 1006
INFORMATION DISCLOSURE CITATION		Applicant(s) MISSELWITZ, et al.			

U.S. PATENT DOCUMENTS

*		DOCUMENT NO.							DATE MM/DD/YY	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
/J.K./	U1	20	03	15	3	6	1	0	08/17/06	Straub, et al.	514	376	
	U2												

FOREIGN PATENT DOCUMENTS

		DOCUMENT NO.							DATE DD/MM/YY	COUNTRY	PRIMARY CLASS	SUB-CLASS	TRANSLATION	
													YES	NO
	F1													

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, etc.)

/J.K./	R1	Kubitza, et al., Multiple dose escalation study investigating the pharmacodyanamics, safety, and pharmacokinetics of BAY 59-7939 an oral, direct Factor Xa inhibitor in healthy male subjects, Blood, Vol 102:11, 16 Nov. 2003, pg. 811a.
/J.K./	R2	Kubitza, et al., ABSTRACT 3010, Single dose escalation study investigating the pharmacodyanamics, safety, and pharmacokinetics of BAY 59-7939 an oral, direct Factor Xa inhibitor in healthy male subjects, Blood, Vol 102:11, 16 Nov. 2003, pg. 813a.
	R3	.

EXAMINER	/Jody Karol/	DATE CONSIDERED 03/10/2011

* EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

PTO/SB/08b (08-08)
Approved for use through 08/31/2008. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 10

Complete if Known	
Application Number	11/883,218-Conf. #9960
Filing Date	July 27, 2008
First Named Inventor	Witz Missel
Art Unit	N/A
Examiner Name	Not Yet Assigned
Attorney Docket Number	11987-00042-US

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
/J.K./	AA*	US-2,811,555	10-29-1957	Larive, et al.	
/J.K./	AB*	US-3,279,880	10-18-1966	Straley et al.	
/J.K./	AC*	US-4,250,318	02-10-1981	Dostert et al.	
/J.K./	AD*	US-4,128,654	12-05-1978	Fugitt et al.	
/J.K./	AE*	US-4,327,725	05-04-1982	Cortese et al.	
/J.K./	AF*	US-4,500,519	02-19-1985	Lormeau, et al.	
/J.K./	AG*	US-4,705,779	11-10-1987	Madi-Szabo, et al.	
/J.K./	AH*	US-4,765,989	08-23-1988	Wong et al.	
/J.K./	AI*	US-4,948,801	08-14-1990	Carlson et al.	
/J.K./	AJ*	US-4,977,173	12-11-1990	Brittelli et al.	
/J.K./	AK*	US-5,002,937	03-26-1991	Bosies et al.	
/J.K./	AL*	US-5,254,577	10-19-1993	Carlson, et al.	
/J.K./	AM*	US-5,349,045	09-20-1994	Ying Jiang	
/J.K./	AN*	US-5,532,255	07-02-1996	Raddatz et al.	
/J.K./	AO*	US-5,561,148	10-01-1996	Gante et al.	
/J.K./	AP*	US-5,565,571	10-01-1996	Barbachyn et al.	
/J.K./	AQ*	US-5,654,428	08-05-1997	Barbachyn et al.	
/J.K./	AR*	US-5,654,435	08-05-1997	Barbachyn et al.	
/J.K./	AS*	US-5,688,792	11-18-1997	Barbachyn, et al.	
/J.K./	AT*	US-5,756,732	05-26-1998	Barbachyn et al.	
/J.K./	AU*	US-5,792,765	08-11-1998	Riedl, et al.	
/J.K./	AV*	US-5,801,246	09-01-1998	Barbachyn et al.	
/J.K./	AW*	US-5,827,857	10-27-1998	Riedl, et al.	
/J.K./	AX*	US-5,910,504	06-08-1999	Hutchinson, et al.	
/J.K./	AY*	US-5,922,708	07-13-1999	Riedl, et al.	
/J.K./	AZ*	US-5,929,248	07-27-1999	Barbachyn et al.	
/J.K./	AA1*	US-5,935,724	08-10-1999	Spillman et al.	
/J.K./	AB1*	US-5,972,947	10-26-1999	Tsaklakidis et al.	
/J.K./	AC1*	US-5,977,373	11-02-1999	Gadwood et al.	
/J.K./	AD1*	US-5,998,406	12-07-1999	Hester et al.	
/J.K./	AE1*	US-6,069,160	05-30-2000	Stolle, et al.	
/J.K./	AF1*	US-6,159,997	12-12-2000	Tsujita et al.	
/J.K./	AG1*	US-6,218,413	04-17-2001	Hester et al.	
/J.K./	AH1*	US-6,251,869	06-26-2001	Michael J. Bohanon	
/J.K./	AI1*	US-6,265,178	07-24-2001	Martin, Jr.	
/J.K./	AJ1*	US-6,281,210	08-28-2001	Hester, Jr.	
/J.K./	AK1*	US-6,294,201-B1	09-25-2001	Kettelhoit et al	
/J.K./	AL1*	US-2001/0029351-A1	10-11-2001	Falotico et al.	
/J.K./	AM1*	US-2001/0046987-A1	11-29-2001	Hester et al.	
/J.K./	AN1*	US-2003/0161882-A1	08-28-2003	Waterman	
/J.K./	AO1*	US-2004/0162427-A1	08-19-2004	Rosentreter et al.	
/J.K./	AP1*	US-6,805,881-B1	10-19-2004	Kanikanti et al.	
/J.K./	AQ1*	US-6,818,243-B2	11-16-2004	Nagashima et al.	
/J.K./	AR1*	US-2004/0242660-A1	12-02-2004	Straub et al.	
/J.K./	AS1*	US-2005/0064006-A1	03-24-2005	Perzborn et al.	
/J.K./	AT1*	US-2005/0182055-A1	08-18-2005	Berwe et al.	

630814_1

/Jody Karol/ 03/10/2011

PTO/SB/08b (08-08)
Approved for use through 08/31/2008. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 10

Complete if Known	
Application Number	11/883,218-Conf. #9960
Filing Date	July 27, 2008
First Named Inventor	Witz Missel
Art Unit	N/A
Examiner Name	Not Yet Assigned
Attorney Docket Number	11987-00042-US

/J.K./	AU1*	US-2005/0261502-A1	11-24-2005	Straub et al.	
/J.K./	AV1*	US-7,034,017-B2	04-25-2006	Straub et al.	
/J.K./	AW1*	US-7,045,631-B2	04-25-2006	Straub et al.	
/J.K./	AX1*	US-2006/0154969-A1	07-13-2006	Rosentreter et al.	
/J.K./	AY1*	US-7,078,417-B2	07-18-2006	Rosentreter et al.	
/J.K./	AZ1*	US-7,109,218-B2	09-19-2006	Rosentreter et al.	
/J.K./	AA2*	US-7,129,255-B2	10-31-2006	Rosentreter et al.	
/J.K./	AB2*	US-2006/0258724-A1	11-16-2006	Straub et al.	
/J.K./	AC2*	US-2007/0026065-A1	02-01-2007	Benke et al.	
/J.K./	AD2*	US-2007/0149522-A1	06-28-2007	Thomas	
/J.K./	AE2*	US-2008/0026057-A1	01-31-2008	Benke	
/J.K./	AF2*	US-2008/0090815-A1	04-17-2008	Straub et al.	
/J.K./	AG2*	US-2008/0200674-A1	08-21-2008	Straub et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document: Country Code[3]-Number[4]-Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
/J.K./	BA	DE-2836305-A1	03-01-1979	Delalande SA		See US 4250318
/J.K./	BB	GB-2140687	12-05-1984	Alza Corp.		
/J.K./	BC	EP-0 127 902 A2	12-12-1984	E.I. Du Pont de Nemours and Co.		See US 4705799
/J.K./	BD	EP-0 316 594 A1	05-24-1989	The Du Pont Merck Pharmaceutical Co.		See US 4977173
/J.K./	BE	EP-0350002-A1	01-10-1990	Boehringer Mannheim GmbH		See US 5002937
/J.K./	BF	EP-0 352 781 A2	01-31-1990	E.I. Du Pont De Nemours and Co.		See US 4948801
/J.K./	BG	WO-93/09103 A1	05-13-1993	The Upjohn Company		See US 5565571
/J.K./	BH	WO-93/23384-A1	11-25-1993	The UpJohn Company		
/J.K./	BI	EP-0623615-A1	11-09-1994	Merck Patent GmbH		See US 5532255
/J.K./	BJ	EP-0645376 A1	03-29-1995	Merck Patent GmbH		See US 5561148
/J.K./	BK	EP-0738726-A1	10-23-1996	Bayer AG		See US 6069160
/J.K./	BL	WO-97/03072-A1	01-31-1997	Boehringer Mannheim GmbH		See US 5972947
/J.K./	BM	WO-97/09328 A1	03-13-1997	Pharmacia & Upjohn Company		See US 5935724
/J.K./	BN	WO-97/10223-A1	03-20-1997	Pharmacia & UpJohn Company		
/J.K./	BO	EP-0 785 200 A2	07-23-1997	Bayer AG		See US 5827857
/J.K./	BP	DE-196 04 223 A1	08-07-1997	Bayer AG		See US 5792765
/J.K./	BQ	WO-98/01446-A1	01-15-1998	Zeneca Limited		
/J.K./	BR	WO-98/54161 A1	12-03-1998	Pharmacia & Upjohn Company		See US 6218413
/J.K./	BS	WO-99/02525 A1	01-21-1999	Pharmacia & Upjohn Company		See US 5977373
/J.K./	BT	WO-99/03846 A1	01-28-1999	Bayer Aktiengesellschaft		See Abstract
/J.K./	BU	WO-99/21535-A1	05-06-1999	Bayer Aktiengesellschaft		See US 6294201 B1
/J.K./	BV	WO-99/24428 A1	05-20-1999	Pharmacia & Upjohn Company		See US 5998406
/J.K./	BW	WO-99/29688 A1	06-17-1999	Pharmacia & Upjohn Company		See US 6265178
/J.K./	BX	WO-99/31092-A1	06-24-1999	Merck Patent GmbH		See Abstract

630814_1

/Jody Karol/ 03/10/2011

PTO/SB/08b (08-08)
Approved for use through 08/31/2008. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 3 of 10

Complete if Known	
Application Number	11/883,218-Conf. #9960
Filing Date	July 27, 2008
First Named Inventor	Witz Missel
Art Unit	N/A
Examiner Name	Not Yet Assigned
Attorney Docket Number	11987-00042-US

/J.K./	BY	EP-0930076-A1	07-21-1999	Sankyo Company Limited		
/J.K./	BZ	WO-99/37304-A1	07-29-1999	Rhone-Poulenc Rorer Pharmaceuticals		
/J.K./	BA1	WO-99/37630-A1	07-29-1999	Versicor, Inc.		
/J.K./	BB1	WO-99/40094-A1	08-12-1999	Bayer Aktiengesellschaft		See Abstract
/J.K./	BC1	EP-0950386-A2	10-20-1999	Cordis Corporation		
/J.K./	BD1	WO-99/59616-A1	11-25-1999	Pharmacia & UpJohn Company		
/J.K./	BE1	WO-00/16748-A1	03-30-2000	Bayer AG		See US 6805881 B1
/J.K./	BF1	WO-01/42242-A1	06-14-2001	Ortho-McNeil Pharmaceutical, Inc.		
/J.K./	BG1	WO-01/44212-A1	06-21-2001	Pharmacia & UpJohn Company		See US 6281210 B2
/J.K./	BH1	WO-01/46185-A1	06-28-2001	Pharmacia & UpJohn Company		See US 2001/0046987 A1
/J.K./	BI1	WO-01-47949-A1	07-05-2001	Ajinomoto Co., Inc.		See US 6818243 B2
/J.K./	BJ1	DE-19962924-A1	07-05-2001	Bayer AG		See US 7157456 B2
/J.K./	BK1	AU-744002	02-14-2002	Merck Patent GmbH		
/J.K./	BL1	WO-02/25210-A1	03-28-2002	Sht Co., Ltd.		
/J.K./	BM1	DE-10105989-A1	08-14-2002	Bayer AG		See US 7034017 B2
/J.K./	BN1	WO-02/064575-A1	08-22-2002	Bayer AG		See US 7034017 B2
/J.K./	BO1	WO-02/070520-A1	09-12-2002	Bayer Aktiengesellschaft		See US 2004/0162427 A1
/J.K./	BP1	WO-02/070484-A1	09-12-2002	Bayer Aktiengesellschaft		See US 2005/0261502 A1
/J.K./	BQ1	WO-02/070485-A1	09-12-2002	Bayer Aktiengesellschaft		See US 2006/0154969 A1
/J.K./	BR1	WO-02/079195-A1	10-10-2002	Bayer Aktiengesellschaft		See US 7,078,417 B2
/J.K./	BS1	WO-02/079196-A1	10-10-2002	Bayer Aktiengesellschaft		See US 7,129,255 B2
/J.K./	BT1	DE-10129725-A1	01-02-2003	Bayer AG		See US 2004/242660 A1
/J.K./	BU1	WO-03/000256-A1	01-03-2003	Bayer HealthCare AG		See US 2004/242660 A1
/J.K./	BV1	WO-03/08384-A1	01-30-2003	Bayer Aktiengesellschaft		See US 7,045,631 B2
/J.K./	BW1	WO-03/035133-A1	05-01-2003	Bayer HealthCare AG et al.		See US 2005/064006 A1
/J.K./	BX1	WO-03/053441-A1	07-03-2003	Bayer Aktiengesellschaft		See US 7,109,218 B2
/J.K./	BY1	WO-2004/060887-A1	07-22-2004	Bayer HealthCare AG et al.		See US 2007/149522 A1
/J.K./	BZ1	WO-2005/060940-A1	05-07-2005	Bayer HealthCare AG et al.		See US 2008/026057 A1
/J.K./	BA2	DE-10355461-A1	06-23-2005	Bayer HealthCare AG et al.		See US 2008/026057 A1
/J.K./	BB2	WO-2006/072367-A1	07-13-2006	Bayer HealthCare AG et al.		See US 2007/026065 A1
/J.K./	BC2	WO-2005/068456-A1	07-28-2005	Bayer HealthCare AG et al.		See US 7351823 B2

630814_1

/Jody Karol/ 03/10/2011

PTO/SB/08b (08-08)
Approved for use through 08/31/2008. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 4 of 10

	Complete if Known
Application Number	11/883,218-Conf. #9960
Filing Date	July 27, 2008
First Named Inventor	Witz Missel
Art Unit	N/A
Examiner Name	Not Yet Assigned
Attorney Docket Number	11987-00042-US

/J.K./	BD2	WO-2006/079474-A1	08-03-2006	Bayer HealthCare AG et al.		
/J.K./	BE2	WO-2007/036306-A1	04-05-2007	Bayer HealthCare AG et al.		See Abstract
/J.K./	BF2	WO-2007/039134-A1	04-12-2007	Bayer HealthCare AG et al.		See Abstract
/J.K./	BG2	WO-2007/039132-A1	04-12-2007	Bayer HealthCare AG et al.		See Abstract
/J.K./	BH2	WO-2007/039122-A2	04-12-2007	Bayer HealthCare AG et al.		See Abstract
/J.K./	BI2	WO-2007/042146-A1	04-19-2007	Bayer HealthCare AG et al.		See Abstract
/J.K./	BJ2	WO-2008/012002-A1	01-31-2008	Bayer HealthCare AG et al.		See Abstract
/J.K./	BK2	WO-2008/052671-A1	05-08-2008	Bayer HealthCare AG et al.		See Abstract

BM2

Examiner Signature	/Jody Karol/	Date Considered	03/10/2011

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. * CITE NO.: Those application(s) which are marked with an single asterisk (*) next to the Cite No. are not supplied (under 37 CFR 1.98(a)(2)(iii)) because that application was filed after June 30, 2003 or is available in the IFW. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

630814_1

PTO/SB/08b (08-08)
Approved for use through 08/31/2008. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet	5	of	10

Complete if Known	
Application Number	11/883,218-Conf. #9960
Filing Date	July 27, 2008
First Named Inventor	Witz Missel
Art Unit	N/A
Examiner Name	Not Yet Assigned
Attorney Docket Number	11987-00042-US

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
/J.K./	CA	BONO, F., et al., "Human Umbilical Vein Endothelial Cells Express High Affinity Receptors for Factor Xa", Journal of Cellular Physiology, 1997, Vol. 172, pp. 36-43.	
/J.K./	CB	COCKS, T. M., et al., "Protease-Activated Receptors: Sentries for Inflammation", Tips, 2000, Vol. 21, pp. 103-108.	
/J.K./	CC	ROSS, R., "Atherosclerosis- An Inflammatory Disease", New England J. of Medicine, 1999, Vol. 340, No. 2, pp. 115-126.	
/J.K./	CD	NAKATA, M., et al., "DX9065a an Xa Inhibitor, Inhibits Prothrombin-Induced A549 Lung Adenocarcinoma Cell Proliferation", Cancer Letters, 1998, Vol. 122, pp. 127-133.	
/J.K./	CE	KAISER, B., et al., "A Synthetic Inhibitor of Factor Xa, DX-9065a, Reduces Proliferation of Vascular Smooth Muscle Cells in Vivo in Rats", Thrombosis Research, 2000, Vol. 98, pp. 175-185.	
/J.K./	CF	ALTIERI, D. C., et al., "Identification of Effector Cell Protease Receptor-1", The Journal of Immunology, 1990, Vol. 145, No. 1, pp. 246-253.	
/J.K./	CG	COUGHLIN, S. R., "Thrombin Signalling and Protease-Activated Receptors", Nature, 2000, Vol. 407, pp. 258-264.	
/J.K./	CH	ORNSTEIN, D. L., et al., "Cancer, Thrombosis, and Anticoagulants", Current Opinion in Pulmonary Medicine, 2000, Vol. 6, pp. 301-308.	
/J.K./	CI	DABBAGH, K., et al., "Thrombin Stimulates Smooth Muscle Cell Procollagen Synthesis and mRNA Levels via a PAR-1 Mediated Mechanism", Thrombasis and Haemostasis, vol. 79, no.2 1997, pp. 405-409.	
/J.K./	CJ	HERAULT, J-P., et al., "Activation of Human Vascular Endothelial Cells by Factor Xa: Effect of Specific Inhibitors", Biochemical Pharmacology, 1999, Vol. 57, pp. 603-610.	
/J.K./	CK	LEVEUGLE, B., et al., "Heparin Oligosaccharides that Pass the Blood- Brain Barrier Inhibit β-Amyloid Precursor Protein Secretion and Heparin Binding to β-Amyloid Peptide", Journal of Neurochemistry, 1998, Vol. 70, No. 2, pp. 736-744.	
/J.K./	CL	MOLINO, M., et al., "Differential Expression of Functional Protease-Activated Receptor-2 (PAR-2) in Human Vascular Smooth Muscle Cells", Arteriosclerosis, Thrombasis, and Vascular Biology, vol. 18, no. 5, 1998, pp. 825-832.	
/J.K./	CM	PLESCIA, J., et al., "Activation of MAC-1 (CD11b/CD18)-Bound Factor X by Release Cathepsin G Defines an Alternative Pathway of Leucocyte Initiation of Coagulation", Biochem. J., 1996, Vol. 319, pp. 873-879.	
/J.K./	CN	HOWELLS, G. L., et al., "Proteinase-Activated Receptor-2: Expression by Human Neutrophils", Journal of Cell Science, 1997, Vol. 110, pp. 881-887.	
/J.K./	CO	HERBERT, J.-M., et al., "Effector Protease Receptor 1 Mediates the Mitogenic Activity of Factor Xa for Vascular Smooth Muscle Cells in Vitro and In Vivo", J. Clin. Invest., 1998, Vol. 101, no. 5, pp. 993-1000.	
/J.K./	CP	DONNELLY, K. M., et al., "*Ancylostoma caninum* Anticoagulant Peptide Blocks Metastasis In Vivo and Inhibits Factor Xa Binding to Melanoma Cells In Vitro", Thromb Haemost, 1998, Vol. 79, pp. 1041-1047.	
/J.K./	CQ	RAGOSTA, M., et al., "Specific Factor Xa Inhibition Reduces Restenosis After Balloon Angioplasty of Atherosclerotic Femoral Arteries in Rabbits", Circulation, 1994, Vol. 89, No. 3, pp. 1262-1271.	
/J.K./	CR	ZHANG, Y., et al., "Tissue Factor Controls the Balance of Angiogenic and Antiangiogenic Properties of Tumor Cells in Mice", J. Clin. Invest., 1994, Vol. 94, pp. 1320-1327.	

630814_1

/Jody Karol/ 03/10/2011

PTO/SB/08b (08-08)
Approved for use through 08/31/2008. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 6 of 10

Complete if Known	
Application Number	11/883,218-Conf. #9960
Filing Date	July 27, 2008
First Named Inventor	Witz Missel
Art Unit	N/A
Examiner Name	Not Yet Assigned
Attorney Docket Number	11987-00042-US

/J.K./	CS	GREEN, D., et al., "Lower Mortality in Cancer Patients Treated with Low-Molecular-Weight Versus Standard Heparin", The Lancet, 1992, Vol. 339, p. 1476.	
/J.K./	CT	KO, F. N., et al., "Coagulation Factor Xa Stimulates Platelet-Derived Growth Factor Release and Mitogenesis in Cultured Vascular Smooth Muscle Cells of Rat", J. Clin. Invest., 1996, Vol. 98, No. 6, pp. 1493-1501.	
/J.K./	CU	KAKKAR, A. K., et al., "Antithrombotic Therapy in Cancer", BMJ, 1999, Vol. 3318, pp. 1571-1572.	
/J.K./	CV	GASIC, G. P., et al., "Coagulation Factors X, Xa, and Protein S as Potent Mitogens of Cultured Aortic Smooth Muscle Cells", Proc. Natl. Acad. Sci. USA, 1992, Vol. 89, pp. 2317-2320.	
/J.K./	CW	CIRINO, G., et al., "Factor Xa as an Interface Between Coagulation and Inflammation: Molecular Mimicry of Factor Xa Association with Effector Cell Protease Receptor-1 Induces Acute Inflammation In Vivo", J. Clin. Invest., 1997, Vol. 99, No. 10, pp. 2446-2451.	
/J.K./	CX	SENDEN, N. H. M., et al., "Factor Xa Induces Cytokine Production and Expression of Adhesion Molecules by Human Umbilical Vein Endothelial Cells", The Journal of Immunology, 1998, Vol. 161, pp. 4318-4324.	
/J.K./	CY	PAPAPETROPOULOS, A., et al., "Hypotension and Inflammatory Cytokine Gene Expression Triggered by Factor Xa-Nitric Oxide Signaling", Proc. Natl. Acad. Sci. USA, 1998, Vol. 95, pp. 4738-4742.	
/J.K./	CZ	CAMERER, E., et al., "Tissue Factor- and Factor X-dependent Activation of Protease-Activated Receptor 2 by Factor VIIa", PNAS, 2000, Vol. 97, No. 10, pp. 5255-5260.	
/J.K./	CA1	DONOVAN, F. M., et al., "Thrombin Induces Apoptosis in Cultured Neurons and Astrocytes via a Pathway Requiring Tyrosine Kinase and RhaA Activities", The Journal of Neuroscience, 1997, Vol. 17, No. 14, pp. 5316-5326.	
/J.K./	CB1	LINDNER, J. R., et al., "Delayed Onset of Inflammation in Protease-Activated Receptor-2-Deficient Mice", The Journal of Immunology, 2000, pp. 6504-6510.	
/J.K./	CC1	BOUCHARD, B. A., et al., "Effector Cell Protease Receptor-1, a Platelet Activation-dependent Membrane Protein, Regulates Prothrombinase-catalyzed Thrombin Generation", The Journal of Biological Chemistry, 1997, Vol. 272, No. 14, pp. 9244-9251.	
/J.K./	CD1	MOLINO, M., et al., "Endothelial Cell Thrombin Receptors and PAR-2", The Journal of Biological Chemistry, 1997, Vol. 272, No. 17, pp. 11133-11141.	
/J.K./	CE1	NICHOLSON, A. C., et al., "Effector Cell Protease Receptor-1 Is a Vascular Receptor for Coagulation Factor Xa", The Journal of Biological Chemistry, 1996, Vol. 271, No. 45, pp. 28407-28413.	
/J.K./	CF1	WATSON, D. J., et al., "Heparin-Binding Properties of the Amyloidogenic Peptides Aβ and Amylin", The Journal of Biological Chemistry, 1997, Vol. 272, No. 50, pp. 31617-31624.	
/J.K./	CG1	TUSZYNSKI, G. P., et al., "Isolation and Characterization of Antistasin", The Journal of Biological Chemistry, 1987, Vol. 262, No. 20, pp. 9718-9723.	
/J.K./	CH1	KRANZHÖFER, R., et al., "Thrombin Potently Stimulates Cytokine Production in Human Vascular Smooth Muscle Cells but Not in Mononuclear Phagocytes", Circulation Research, 1996, Vol. 79, No. 2, pp. 286-294.	
/J.K./	CI1	SCHWARTZ, R. S., et al., "Neointimal Thickening After Severe Coronary Artery Injury is Limited by Short-term Administration of a Factor Xa Inhibitor", Circulation, 1996, Vol. 93, No. 8, pp. 1542-1548.	
/J.K./	CJ1	ABENDSCHEIN, D. R., et al., "Inhibition of Thrombin Attenuates Stenosis After Arterial Injury in Minipigs", JACC, 1996, Vol. 28, No. 7, pp. 1849-1855.	
/J.K./	CK1	CARMELIET, P., et al., "Gene Manipulation and Transfer of the Plasinogen and Coagulation System in Mice", Seminars in Thrombosis and Hemostasis, 1996, Vol. 22, No. 6, pp. 525-542.	
/J.K./	CL1	STOUFFER, G. A., et al., "The Role of Secondary Growth Factor Production in Thrombin-Induced Proliferation of Vascular Smooth Muscle Cells", Seminars in Thrombosis and	

630814_1

/Jody Karol/ 03/10/2011

PTO/SB/08b (08-08)
Approved for use through 08/31/2008. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 7 of 10

Complete if Known	
Application Number	11/883,218-Conf. #9960
Filing Date	July 27, 2008
First Named Inventor	Witz Missel
Art Unit	N/A
Examiner Name	Not Yet Assigned
Attorney Docket Number	11987-00042-US

		Hemostasis, 1998, Vol. 24, No. 2, pp. 145-150.	
/J.K./	CM1	BEVILACQUA, M. P., et al., "Inducible Endothelial Functions in Inflammation and Coagulation", Seminars in Thrombosis and Hemostasis, 1987, Vol. 13, No. 4, pp. 425-433.	
/J.K./	CN1	RIEDL, B., et al., "Recent Developments with Oxazolidinone Antibiotics", Exp. Opin. Ther. Patents, 1999, Vol. 9, No. 5, pp. 625-633.	
/J.K./	CO1	BARBACHYN, M.R., et al., "Identification of Novel Oxazolidinone (U-100480) with Potent Antimycobacterial Activity", J. Med. Chem., 1996, Vol. 39, pp. 680-685.	
/J.K./	CP1	TUCKER, J. A., et al, "Piperazinyl Oxazolidinone Antibacterial Agents Containing a Pyridine, Diazene, or Triazene Heteroaromatic Ring", J. Med. Chem. 1998, Vol. 41, pp. 3727-3735.	
/J.K./	CQ1	BRICKNER, S.J., et al., "Synthesis and Antibacterial Activity of U-100592 and U-100766, Two Oxazolidinone Antibacterial Agents for the Potenial treatment of Multidrug-Resistant Gram-Positive Bacterial Infections" J. Med. Chem., 1996, Vol. 39, pp. 673-679	
/J.K./	CR1	GREGORY, W.A., et al., "Antibacterials. Synthesis and Structure-Activity Studies of 3-Aryl-2-oxooxazolidines. 1. The "B" Group", J. Med. Chem., 1989, Vol. 32, No. 8, pp. 1673-1681.	
/J.K./	CS1	BERRY, C. N., et al., "Antithrombotic Actions of Argatroban in Rat Models of Venous, 'Mixed' and Arterial Thrombosis, and its Effects on the Tail Transection Bleeding Time", Br. J. Pharmacol., 1994, Vol. 113, pp. 1209-1214.	
/J.K./	CT1	MENG, K., et al., "Effect of Acetylsalicyclic Acid of Experimentally Induced Arterial Thrombosis in Rats", Naunyn-Schmiedeberg's Arch. Pharmacol.,1977, Vol. 301, pp. 115-119.	
/J.K./	CU1	CHERN, J.W., et al., "Studies on Quinazolines IX:[1] Fluorination Versus 1,2-Migration on the Reaction of 1,3-Bifunctionalized Amino-2-Propanol with DAST", Tetrahedron Lett., 1998, Vol. 39, pp. 8483-8486.	
/J.K./	CV1	SHAKESPEARE, W. C., et al., "Palladium-Catalyzed Coupling of Lactams with Bromobenzenes", Tetrahedron Lett., 1999, Vol. 40, pp. 2035*2038.	
/J.K./	CW1	RENGER, B., et al., "Direkte *N*-Arylierung von Amiden: Eine Verbesserung der Goldberg-Reaktion", Synthesis, 1985, pp. 856-860.	
/J.K./	CX1	AEBISCHER, E., et al., "Synthesis of *N*-Arylrolipram Derivatives - Potent and Selective Phosphodiesterase-IV Inhibitors - by Copper Catalyzed Lactam-Aryl Halide Coupling", Hetercycles, 1998, Vol. 48, No. 11 , pp. 2225-2229.	
/J.K./	CY1	PFEIL, E., et al., "β-Aminoäthylierung von Indol und 2-methylindol", Angew Chem., 1967, Vol. 79, No. 4, pp. 188-189.	
/J.K./	CZ1	ZIEGLER, C. B., et al., "Synthesis of Some Novel 7-Substituted Quinolonecarboxylic Acids *via* Nitroso and Nitrone Cycloadditions", J. Hetercycl. Chem., 1988, Vol. 25, No. 2, pp. 719-723.	
/J.K./	CA2	BARTOLI, G., et al, "Electronic and Steric Effects in Nucleophilic Aromatic Substitution. Reaction by Phenoxides as Nucleophiles in Dimethyl Sulfoxide", J. Org. Chem., 1975, Vol. 40, No. 7, pp. 872-874.	
/J.K./	CB2	REPPE, et al., "*N-p-Merthoxyphenyl-pyrrolidon*", Justus Liebigs Ann. Chem., 1955 Vol. 596, p. 208.	
/J.K./	CC2	LUVALLE, J.E., et al., "Oxidation Processes. XXI.[1] The Autoxidation of the ρ-Phenylenediamines", J. Am. Chem. Soc., 1948, Vol. 70, pp. 2223-2233.	
/J.K./	CD2	SNYDER, H.R., et al., "Imidazo[4,5*f*]quinolines III: Antibacterial 7-Methyl-9-(substituted Arylamino)imidazo[4,5-*f*]quinolines", J. Pharm. Sci., 1977, Vol. 66, pp. 1204-1406.	
/J.K./	CE2	ADAMS, R., et al., "Sulfanilamide Derivatives. I", J. Am. Chem. Soc. 1939, Vol. 61, pp. 2342-2349.	
/J.K./	CF2	KHANNA, I.K. , et al., "1,2-Diarylpyrroles as Potent and Selective Inhibitors of Cyclooxygenase-2", J. Med. Chem., 1997, Vol. 40 , pp. 1619-1633.	
/J.K./	CG2	GUTCAIT, A., et al., "Studies on Quinazolines. 6.[1] Asymmetric Synthesis of (S)-(+)- and (R)-(-)-3-[[4-(2-Methoxyphenyl)piperazin-1-yl]methylthio-2,3,-dihydromidazo[1,2-c]quinazolines",	

630814_1

/Jody Karol/ 03/10/2011

PTO/SB/08b (08-08)
Approved for use through 08/31/2008. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 8 of 10

Complete if Known	
Application Number	11/883,218-Conf. #9960
Filing Date	July 27, 2008
First Named Inventor	Witz Missel
Art Unit	N/A
Examiner Name	Not Yet Assigned
Attorney Docket Number	11987-00042-US

		Tetrahedron Asym., 1996, Vol. 7, No. 6, pp. 1641-1648.	
/J.K./	CH2	GRELL, W., et al., "Repaglinide and Related Hypoglycemic Benzoic Acid Derivatives", J. Med. Chem., 1998, Vol. 41, pp. 5219-5246.	
/J.K./	CI2	ARTICO, M. et al., "Rsearch on Compounds with Antiblastic Activity", Farmaco Ed. Sci. 1969, Vol. 24, pp. 179-190.	
/J.K./	CJ2	DANKWARDT, S. M., et al., "Nonpeptide Bradykinin Antagonist Analogs based on a Model of a Sterling-Winthrop Nonpeptide Bradykinin Antagonist Overlapped with Cyclic Hexapeptide Bradykinin Antagonist Peptides", Bioorg. Med. Chem. Lett., 1997, Vol. 7, No. 14, pp. 1921-1926.	
/J.K./	CK2	REPPE, et al., "*N-6-Aminohexyl-pyrrolidon*", Justus Liebigs Ann. Chem. 1955, Vol. 596, pp. 204.	
/J.K./	CL2	BOUCHET, P., et al., "σ Values of *N*-Substitutes Azoles", J. Chem. Soc. Perkin Trans., 1974, Vol. 2, pp. 449-451.	
/J.K./	CM2	SURREY, A. R., et al., "The Preparation of N-Benzyl-3-Morpholones and N-Benzyl-3-Homomorpholones from N-(Hydroxyalkyl)-chloroacetamides" J. Amer. Chem. Soc., 1955, Vol. 77, pp. 633-636.	
/J.K./	CN2	TONG, L.K.J., et al., "The Mechanism of Dye Formation in Color Photography. VII. Intermediate Bases in the Deamination of Quinonediimines" J. Amer. Chem. Soc. 1960, Vol. 82, 1988-2001.	
/J.K./	CO2	DELANDE, S.A., "Heterocycles", Chemical Abstracts, American Chemical Society, 1979, Vol. 90, pp. 663.	
/J.K./	CP2	BOTS, M., et al., Coagulation and Fibrinolysis Markers and Risk of Dementia," Haemostasis, Vol. 28 (1998); pp. 216-222.	
/J.K./	CQ2	BENZAKOUR, O., et al., "Cellular and molecular events in atherogenesis; basis for pharmocological and gene therapy approaches to stenosis," Cellular Pharmacology, 1996, Vol 3, pp. 7-22.	
/J.K./	CR2	KANTHOU, C., et al., "Cellular effects of thrombin and their signalling pathways," Cellular Pharmacology, Vol. 2 (1995); pp. 293-302.	
/J.K./	CS2	KAISER, B., et al., "Antiproliferation Action of Factor Xa Inhibitors in a Rat Model of Chronic Restenosis," Abstracts of the XVIIth Congress of the International Society on Thrombosis and Haemostasis, August 1999, p. 144.	
/J.K./	CT2	TYRRELL, D., et al., "Heparin in Inflammation: Potential Therapeutic Applications Beyond Anticoagulation," Advances in Pharmacology, Vol. 46 (1999); pp. 151-208.	
/J.K./	CU2	SMIROVA, I., et al., "Thrombin Is an Extracellular Signal that Activates Intracellular Death Protease Pathways Inducing Apoptosis in Model Motor Neurons," J. Neurobiology, Vol. 36 (1998); pp. 64-80.	
/J.K./	CV2	BONO, F., et al., "Factor Xa Activates Endothelial Cells by a Receptor Cascade Between EPR-1 and PAR-2," Arterioscler Thromb Vasc Biol., Nov. 2000; pp 1-6.	
/J.K./	CW2	LALA, P. et al, "Role of Nitric Oxide in tumor progression: Lessons Learned from Experimental Tumors," Cancer and Metastasis Review," Vol. 17, pages 91-106 (1998).	
/J.K./	CX2	GOLUB, T., et al., "Molecular Classification of Cancer Science (1999), Vol. 286, 531-537.	
/J.K./	CY2	FDA mulls drug to slow late-stage Alzheimer's [online], [retrieved on 2003-09-23]. Retrieved from the internet, URL:http://www.cnn.com/2003/HEALTH/conditions/09/24/alzheimers.drug.ap/index.html>.	
/J.K./	CZ2	Ullman's Encyclopedia of Industrial Chemistry, Fifth Revised Ed., Editors: Elvers, B., Hawkins, S., VCH Verlagsgesellschaft mbH, Weinheim, 19985-1996, Ch. 5, 488-506.	
/J.K./	CA3	ZHU, B., Scarborough, R., "Recent Advances in Inhibitors of Factor Xa in the Prothrombinase Complex," *Curr. Opinions Card. Pul. Ren. Inv. Drugs,* 1:63-87 (1999).	
/J.K./	CB3	UZAN, A., "Antithrombotic Agents," *Emerging Drugs: The Prospect for Improved Medicines,"*	

630814_1

/Jody Karol/ 03/10/2011

PTO/SB/08b (08-08)
Approved for use through 08/31/2008. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 9 of 10

Complete if Known	
Application Number	11/883,218-Conf. #9960
Filing Date	July 27, 2008
First Named Inventor	Witz Missel
Art Unit	N/A
Examiner Name	Not Yet Assigned
Attorney Docket Number	11987-00042-US

		3: 189-208 (1998).	
/J.K./	CC3	KAISER, B., "Thrombin and Factor Xa Inhibitors," *Drugs of the Future,* 23: 423-426 (1998).	
/J.K./	CD3	AL-OBEIDI, F., Ostrem, J., "Factor Xa Inhibitors," *Expert Opin. Therapeutic Patents,* 9: 931-953 (1999).	
/J.K./	CE3	AL-OBEIDI, F., Ostrem, J., "Factor Xa Inhibitors by Classical and Combinatorial Chemistry," *DDT,* 3: 223-231 (May 1998).	
/J.K./	CF3	HAUPTMANN, J.,et al., "Synthetic Inhibitors of Thrombin and Factor Xa: From Bench to Bedside," *Thrombosis Research* , 93: 203-241 (1999).	
	CG3	Pschyrembel, Klinisches Worterbuch, 257. Auflage, 1994, Walter de Gruyter Verlag, p. 199-200, Stichwort "Blutgerinnung."	
	CH3	Rompp Lexikon Chemie, Ver. 1.5, 1998, Georg Thieme Verlag Stuttgart, Stichwort "Blutgerrinung" Lubert Stryer, Biochemie, Spektrum der Wissenschaft Verlagsgesellschaft mbH Heidelberg, 1990, p. 259.	
	CI3	Pschyrembel, Klinisches Worterbuch, 257. Auflage, 1994, Walter de Gruyter Verlag, p. 610, Stichwort "Heparin."	
	CJ3	Rompp Lexikon Chemie, Ver. 1.5, 1998, Georg Thieme Verlag Stuttgart, Stichwort "Heparin."	
	CK3	Pschyrembel, Klinisches Worterbuch, 257. Auflage, 1994, Walter de Gruyter Verlag, p. 292, Stichwort "Cumarinderivate."	
/J.K./	CL3	BECKER, M.R., et al., "Synthesis, Sar and in Vivo Activity of Novel Thienopyridine Sulfonamide Pyrrolidininones as Factor Xa Inhibitors," *Bioorganic and Medicinal Chemistry Letters,* 9: 2753-2758 (1999).	
/J.K./	CM3	LINDER, J., et al., "Delayed Onset of Inflammation in Protease-Activated Receptor-2-Deficient Mice," J. Immunology, 2000, pp. 6504-6510.	
/J.K./	CN3	CIRINO, G. et al. "Inflammation-Coagulation Network: Are Serine Protease receptors the knot?; Tips; 200, vol.21, pp. 170-172	
/J.K./	CO3	ROEHRIG, S. et al. Discovery of the Novel Antithrombotic Agent 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)thiophene-2-carboxamide (BAY 59-7939): An Oral, Direct Factor Xa Inhibitor. J. Med. Chem. 48, 22. Sept. 2005, pp. 5900-5908.	
/J.K./	CP3	CAIRA, M. Crystalline Polymorphism Of Organic Compounds. Springer Verlag Berlin Heidelberg 198, 1998, pp. 163-208.	
/J.K./	CQ3	HANCOCK, B. et al. Characteristics and Significance of the Amorphous State in Pharmaceutical Systems. Journal of Pharmaceutical Science. 86, 1 (1997-1), pp. 1-12.	
/J.K./	CR3	CHIOU, W.L. et al. Pharmaceutical Applications of Solid Dispersion Systems. Journal of Pharmaceutical Sciences 60, (1971). 128-1302.	
/J.K./	CS3	FORD, J.L. The Current Status of Solid Dispersions. Pharm Acta Helv. 61, (1986)69-88.	
/J.K./	CT3	RASENACK, N. et al. Poorly Water-soluble Drugs for Oral Delivery- A Challenge for Pharmaceutical Development. Pharmazeutische Industrie 67, Nr. 5 (2005), 583-591.	
/J.K./	CU3	BREITENBACH, J. Melt extrusion: from process to drug delivery technology. European Journal of Pharmaceutics and Biopharmaceutics 54 (2002) 107-117.	
	CV3	BREITENBACH, J. Feste Loesungen durch Schmelzextrusion - ein integriertes Herstellkonzept. Pharmazie in unserer Zeit 29 (2000), 46-49.	
/J.K./	CW3	http://familydoctor.org/online/famdocen/home/common/heartdisease/basics/290.html	
/J.K./	CX3	LERK, et al., Effect of Hydrophilization Drugs on Release Rat from Capsules, J. of Pharma. Sciences, 67(7), pp. 935-939 (1978)	
/J.K./	CY3	LERK, et al., *In Vitro and In Vivo* Availability of Hydrophilized Phenytoin from Capsules, J. of Pharma. Sciences, 68(5), pp. 634-638 (1979)	
/J.K./	CZ3	GREAVES, et al., Novel Approaches to the Preparation of Low-Dose Solid Dosage Forms,Pharmaceutical Technology. January, pp. 60-64, (1995)	

630814_1

/Jody Karol/ 03/10/2011

PTO/SB/08b (08-08)
Approved for use through 08/31/2008. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 10 of 10

Complete if Known	
Application Number	11/883,218-Conf. #9960
Filing Date	July 27, 2008
First Named Inventor	Witz Missel
Art Unit	N/A
Examiner Name	Not Yet Assigned
Attorney Docket Number	11987-00042-US

/J.K./	CA4	REPPE, et al., Justus Liebigs Ann. Chem. 596, 1955, p. 209.	
/J.K./	CB4	WONG et al., The Journal of Pharmacology and Expermental Therapeutics, Vol. 295, No. 1 (2000) pages 212-218.	
/J.K./	CC4	[Database Bielstein] Bielstein Institute for Organic Chemistry, Frankfurt-Main, DE. Database Accession No. 8822985.	
/J.K./	CD4	PERZBORN, E. et al. *In vitro* and *in vivo* studies of the novel antithrombotic agent BAY 59-7939-an oral, direct Factor Xa inhibitor. Journal of Thrombosis and Haemostasis 3, 3, March 2005, pp. 514-521.	
/J.K./	CE4	ESPINOSA, G. et al. Thrombotic microangiopathic haemolytic anaemia and antiphospholipid antibodies. Annals of the Rheumatic Diseases, 63, 6, June 2004, pp. 730-736.	
/J.K./	CF4	BONOMINI, V. et al. A New Antithrombotic Agent in the Treatment of Acute Renal Failure Due to Hemolytic-Uremic Syndrome and Thrombotic Thrombocytopenic Purpura. Nephron 37, 1984, 2, 144.	
/J.K./	CG4	SINHA, U. et al. Antithrombotic and hemostatic capacity of factor Xa versus thrombin inhibitors in models of venous and arteriovenous thrombosis. European Journal of Pharmacology 2000, 395, 51-59.	
/J.K./	CH4	BETZ, A. Recent advances in Factor Xa inhibitors. Expert Opinion Ther. Patents 2001, 11, 1007-1017.	
	CI4	TAN, K.T. et al. Factor X inhibitors. Expert Opinion Investig. Drugs 2003, 12, 799-804.	
/J.K./	CJ4	RUEF, J. et al. New antithrombotic drugs on the horizon. Expert Opinion Investig. Drugs 2003, 12, 781-797.	
/J.K./	CK4	SAMAMA, M.L. Synthetic direct and indirect factor Xa inhibitors. Thromobis Research 2002, 106, V267-V273.	
/J.K./	CL4	QUAN, M.L. The race to an orally active Factor Xa inhibitor: Recent advances. Current Opinion in Drug Discovery & Development 2004, 7, 460-469.	
/J.K./	CM4	The Ephesus Study, Blood 2000, 96, 490a	
/J.K./	CN4	The Penthifra Study, Blood 2000, 96, 490a	
/J.K./	CO4	The Pentamaks Study, Blood 2000, 96, 490a-491a.	
/J.K./	CP4	The Pentathlon 2000 Study, Blood 2000, 96, 491a	
/J.K./	CQ4	LEADLEY, R.J. Coagulation Factor Xa Inhibition: Biological Background and Rationale. Current Topics in Medical Chemistry 2001, 1, 151-159.	
/J.K./	CR4	GILLIGAN, D.M. et al. The Management of Atrial Fibrillation. The American Journal of Medicine, vol. 101, (4) 1996, 413-421.	
/J.K./	CS4	KUBITZA, D. et al. Novel factor Xa inhibitors for prevention and treatment of thromboembolic diseases. Expert Opinion on Investig. Drugs, vol. 15, (8) 2006, pp. 843-855.	
/J.K./	CT4	WILLIAMS, E.M. Vaughan. Classificating anti-arrhythimic drugs. In: Cardiac Arrythias-Proceedings of a symposium, sandoe E., soedertaeje: Astra (1970), pp. 449-469.	

Examiner Signature	/Jody Karol/	Date Considered	03/10/2011

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1]Applicant's unique citation designation number (optional). [2]Applicant is to place a check mark here if English language Translation is attached.

630814_1

Docket No.: 11987-00042-US
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Frank Misselwitz et al.

Application No.: 11/883,218 | Confirmation No.: 9960

Filed: July 27, 2007 | Art Unit: 1627

For: PREVENTION AND TREATMENT OF THROMBOEMBOLIC DISORDERS | Examiner: Jody Lynn Karol

RESPONSE TO RESTRICTION REQUIREMENT

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

INTRODUCTORY COMMENTS

Applicants respond to the Office Action mailed November 10, 2010 as follows:

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 4 of this paper.

AMENDMENTS TO THE CLAIMS

1. (original) A method of treating a thromboembolic disorder comprising administering a direct factor Xa inhibitor no more than once daily for at least five consecutive days in an oral dosage form to a patient in need thereof, wherein said inhibitor has a plasma concentration half life of 10 hours or less when orally administered to a human patient.

2. (original) The method of claim 1, wherein one dosage form is administered.

3. (original) The use of an oral dosage form of a direct factor Xa inhibitor for the manufacture of a medicament for the treatment of a thromboembolic disorder administered once daily for at least five consecutive days, wherein said inhibitor has a plasma concentration half life of 10 hours or less when orally administered to a human patient.

4. (currently amended) The method ~~or use as claimed in any of Claims 1 to 3~~ of claim 1, wherein the thromboembolic disorder is ST Segment Elevation Myocardial Infarction (STEMI), Non ST Segment Elevation Myocardial Infarction (NSTEMI), unstable angina, reocclusion after angioplasty or aortocoronary bypass, pulmonary embolisms, deep vein thromboses or stroke.

5. (currently amended) The method ~~or use as claimed in any of Claims 1 to 4~~ of claim 1, wherein the oral dosage form is a rapid-release tablet.

6. (currently amended) The method ~~or use as claimed in any of Claims 1 to 5~~ of claim 1, wherein the direct factor Xa inhibitor is 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide.

7. (original) A packaged pharmaceutical composition comprising a container containing a rapid-release tablet comprising 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide, said

container furthermore containing instructions for using said rapid-release tablet to treat a thromboembolic disorder.

8. (original) The packaged pharmaceutical composition of claim 7, comprising a container containing a rapid-release tablet comprising 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide, said container furthermore containing instructions for administering said rapid-release tablet at a frequency of once daily.

9. (new) The method of claim 2, wherein the thromboembolic disorder is ST Segment Elevation Myocardial Infarction (STEMI), Non ST Segment Elevation Myocardial Infarction (NSTEMI), unstable angina, reocclusion after angioplasty or aortocoronary bypass, pulmonary embolisms, deep vein thromboses or stroke.

10. (new) The method of claim 2, wherein the oral dosage form is a rapid-release tablet.

11. (new) The method of claim 4, wherein the oral dosage form is a rapid-release tablet.

12. (new) The method of claim 2, wherein the direct factor Xa inhibitor is 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide.

13. (new) The method of claim 4, wherein the direct factor Xa inhibitor is 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide.

14. (new) The method of claim 5, wherein the direct factor Xa inhibitor is 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide.

REMARKS

The claims are amended without prejudice or disclaimer to replace multiple dependent claims with dependent claims. Support is found in the originally filed claims. No new matter is added. After entry of this amendment, claims 1-14 are pending.

Applicants respectfully disagree with the restriction requirement. However, to expedite prosecution, Applicants elect Group II, claims 1-2 and 4-6 (in part). After entry of the present amendment, Group II corresponds to claims 1-2, 4-6 and 9-14. Applicants elect the species of deep vein thrombosis and the compound 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide for initial search and consideration. Claims 1-14 are readable on this elected species of compound and disorder.

Applicant believes no fee is due with this paper. However, if a fee is due, please charge our Deposit Account No. 03-2775, under Order No. 11987-00042-US from which the undersigned is authorized to draw.

Dated: December 10, 2010

Respectfully submitted,

Electronic signature: /Christine M. Hansen/
Christine M. Hansen
Registration No.: 40,634
CONNOLLY BOVE LODGE & HUTZ LLP
1007 North Orange Street
P. O. Box 2207
Wilmington, Delaware 19899-2207
(302) 658-9141
Attorney for Applicant

#955689

Electronic Acknowledgement Receipt

EFS ID:	9009876
Application Number:	11883218
International Application Number:	
Confirmation Number:	9960
Title of Invention:	Prevention and Treatment of Thromboembolic Disorders
First Named Inventor/Applicant Name:	Frank Misselwitz
Customer Number:	23416
Filer:	Christine Hansen/Lynn Ferry
Filer Authorized By:	Christine Hansen
Attorney Docket Number:	11987-00042
Receipt Date:	10-DEC-2010
Filing Date:	16-JUL-2008
Time Stamp:	14:02:34
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		Response_to_Restriction_Requirement.pdf	166110 723b6161bbf0522e1ce86f3360bdbad1a83b1d64	yes	4

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Response to Election / Restriction Filed	1	1
	Claims	2	3
	Applicant Arguments/Remarks Made in an Amendment	4	4
Warnings:			
Information:			
	Total Files Size (in bytes):	166110	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
11/883,218	07/16/2008	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☐ RATE ($)	SMALL ENTITY ☐ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT 12/10/2010

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 14	Minus	** 20	= 0	X $ =		OR	X $52=	0
Independent (37 CFR 1.16(h))	* 3	Minus	***3	= 0	X $ =		OR	X $220=	0
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/KIMBERLY PANNELL/

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
11/883,218	07/16/2008	

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☐		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	12/10/2010	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 14	Minus	** 20	= 0	X $ =		OR	X $52=	0
	Independent (37 CFR 1.16(h))	* 3	Minus	***3	= 0	X $ =		OR	X $220=	0
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/KIMBERLY PANNELL/

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/883,218	07/16/2008	Frank Misselwitz	11987-00042	9960

23416 7590 11/10/2010

CONNOLLY BOVE LODGE & HUTZ, LLP
P O BOX 2207
WILMINGTON, DE 19899

EXAMINER	
KAROL, JODY LYNN	

ART UNIT	PAPER NUMBER
1627	

MAIL DATE	DELIVERY MODE
11/10/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	11/883,218	MISSELWITZ ET AL.	
	Examiner	Art Unit	
	Jody L. Karol	1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *1* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 July 2007*.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-8* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) 7-8, drawn to a packaged pharmaceutical composition comprising a container containing a rapid-release tablet comprising 5-chloro-N-([(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl]methyl)-2-thiophenecarboxamide and instructions for using said rapid-release tablet to treat a thromboembolic disorder.

Group II, claim(s) 1-2 and 4-6 (in part), drawn to a method of treating a thromboembolic disorder comprising administering a direct factor Xa inhibitor no more than one daily for at least five consecutive days in an oral dosage form to a patient in need thereof.

Group III, claim(s) 3 and 4-6 (in part), drawn to a method of manufacturing a medicament using an oral dosage form of a direct factor Xa inhibitor. (It is noted that "use of" claims are rejected under 35 U.S.C. 101 and 35 U.S.C. 112, 2nd paragraph for being an improper method/process claim).

2. The groups of inventions listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

An international application should relate to only one invention or, if there is more than one invention, the inclusion of those inventions in one international application is only permitted if all inventions are so linked as to form a single general inventive concept (PCT Rule 13.1). With respect to a group of inventions claimed in an

international application, unity of invention exists only when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding special technical features.

The expression "special technical features" is defined in PCT Rule 13.2 as meaning those technical features that define a contribution which each of the inventions, considered as a whole, makes over the prior art. The determination is made on the contents of the claims as interpreted in light of the description and drawings (if any). Whether or not any particular technical feature makes a "contribution" over the prior art, and therefore constitutes a "special technical feature," should be considered with respect to novelty and inventive step.

The common technical feature among the groups is direct factor Xa inhibitors. The direct factor Xa inhibitor cannot be considered a special technical feature because it is known in the prior art. For example, Straub et al. teach 5-chloro-N-([(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl]methyl)-2-thiophenecarboxamide, the direct factor Xa inhibitor as claimed in the instant claims 6-8 (see US 2003/0153610; page 26, Example 44). Accordingly, the unity of invention is considered to be lacking, and restriction in accordance with the rules of unity of invention is considered proper.

Election of Species

3. This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

The species are as follows:

(1) direct factor Xa inhibitors (i.e. 5-chloro-N-([(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl]methyl)-2-thiophenecarboxamide)

(2) thromboembolic disorders (i.e. pulmonary embolism, stroke, etc.)

Applicant is required, in reply to this action, to elect a single species of (1) direct factor Xa inhibitors and a single species of (2) thromboembolic disorders to which the claims shall be restricted if no generic claim is finally held to be allowable. The reply must also identify the claims readable on the elected species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered non-responsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise require all the limitations of an allowed generic claim. Currently, the following claim(s) are generic: claims 1-3 and 5.

REQUIREMENT FOR UNITY OF INVENTION

As provided in 37 CFR 1.475(a), a national stage application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept ("requirement of unity of invention"). Where a group of inventions is claimed in a national stage application, the requirement of unity of invention shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The expression "special technical

features" shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

The determination whether a group of inventions is so linked as to form a single general inventive concept shall be made without regard to whether the inventions are claimed in separate claims or as alternatives within a single claim. See 37 CFR 1.475(e).

WHEN CLAIMS ARE DIRECTED TO MULTIPLE CATEGORIES OF INVENTIONS

As provided in 37 CFR 1.475(b), a national stage application containing claims to different categories of invention will be considered to have unity of invention if the claims are drawn only to one of the following combinations of categories:

(1) A product and a process specially adapted for the manufacture of said product; or

(2) A product and process of use of said product; or

(3) A product, a process specially adapted for the manufacture of the said product, and a use of the said product; or

(4) A process and an apparatus or means specifically designed for carrying out the said process; or

(5) A product, a process specially adapted for the manufacture of the said product, and an apparatus or means specifically designed for carrying out the said process.

Otherwise, unity of invention might not be present. See 37 CFR 1.475(c).

4. Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species or invention to be examined even though the requirement may be traversed (37 CFR 1.143) and (ii) identification of the claims encompassing the elected invention.

The election of an invention or species may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected invention or species.

Should applicant traverse on the ground that the inventions have unity of invention (37 CFR 1.475(a)), applicant must provide reasons in support thereof. Applicant may submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. Where such evidence or admission is provided by applicant, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

Inventorship Notice

5. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Rejoinder Notice

6. The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder. All claims directed to a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). Additionally, in order to retain the right to rejoinder in accordance with the

above policy, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder**. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Correspondence

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jody L. Karol whose telephone number is (571)270-3283. The examiner can normally be reached on 8:30 am - 5:00 pm Mon-Fri EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

JLK

/Yong S. Chong/
Primary Examiner, Art Unit 1627

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11883218	MISSELWITZ ET AL.
	Examiner	**Art Unit**
	Jody L Karol	1627

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	11/02/2010								
	1	÷								
	2	÷								
	3	÷								
	4	÷								
	5	÷								
	6	÷								
	7	÷								
	8	÷								

PTO/SB/08b (04-09)
Approved for use through 05/31/2009. OMB 0651-0031
U.S. Patent and Trad emark Office; U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 4

Complete if Known	
Application Number	11/883,218-Conf. #9960
Filing Date	July 16, 2008
First Named Inventor	Frank Misselwitz
Art Unit	1615
Examiner Name	Not Yet Assigned
Attorney Docket Number	11987-00042-US

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

NON PATENT LITERATURE DOCUMENTS

Examiner Initials	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journ al, serial, symposium, catalog, etc.), date, page(s) , volume-issue number(s), publisher, city and/or country where published.	T[2]
	CA	WHITE, R.H., "The Epidemiology of Venous Thromboembolism", Circulation, (2003), Vol. 107, (Suppl. 1), pp. I-4 - I-8.	
	CB	FEIGN, V.L., et al., "Stroke Epidemiology: A Review of Population-Based Studies of Incidence, Prevalence, and Case-Fatality in the Late 20th Century", The Lancet Neurology, (2003), Vol. 2, pp. 43-53.	
	CC	FANG, J., et al., "Dissociation of Hospitalization and Mortality Trends for Myocardial Infarction in the United States from 1988 to 1997", The American Journal of Medicine, (2002), Vol. 113, pp. 208-214.	
	CD	RAGHAVEN, S.A.V., et al., "Recent Advances in the Status and Targets of Antithrombotic Agents", Drugs of the Future, (2002), Vo.. 27, No. 7, pp. 669-683.	
	CE	WIELAND, H.A., et al., "Approaches in Anticoagulation: Rationales for Target Positioning", Current Opinion in Investigational Drugs, (2003), Vol. 4, No. 3. pp. 264-271.	
	CF	RIES, U.J., et al., "Serine Proteases as Targets for Antithrombotic Therapy", Drugs of the Future, (2003), Vol. 28, No. 4, pp. 355-370.	
	CG	LINKINS, L-A., et al., "New Anticoagulant Therapy", Annu. Rev. Med., (2005), Vol. 56, pp. 63-77.	
	CH	GOODMAN AND GILLMAN, "The Pharmacological Basis of Therapeutics", 7th Ed., MacMillian Publishing Co., NY, (1985), pp. 27-28.	
	CI	ROWLAND, M., et al., "Multiple-Dose Regimens", Clinical Pharmacokinetics, Concepts and Applications, 3rd Ed, Lea & Febiger, Williams & Wilkins, Media, PA (1995), pp. 83-105.	
	CJ	BIRKETT, D.J., "Why is Half-Life Important", Pharmacokinetics Made Easy, McGraw-Hill Education, (2000), pp. 20-21.	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1]Applicant's unique citation designation number (optional). [2]Applicant is to place a check mark here if English language Translation is attached.

PTO/SB/08b (04-09)
Approved for use through 05/31/2009. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 4

Complete if Known	
Application Number	11/883,218-Conf. #9960
Filing Date	July 16, 2008
First Named Inventor	Frank Misselwitz
Art Unit	1615
Examiner Name	Not Yet Assigned
Attorney Docket Number	11987-00042-US

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	CK	ROEHRIG, S., et al., "Discovery of the Novel Antithrombotic Agent Bay 59-7939, an Orally Active, Direct Factor XA Inhibitor", 228th ACS National Meeting, (2004), MEDI-156.	
	CL	GEERTS, W.H., et al., "Prevention of Venous Thromboembolism", Chest, (2001), Vol. 119, pp. 132S-175S.	
	CM	TAKEHANA, S., et al., "Antithrombotic Effect of AX1826, A Novel Inhibitor of Factor Xa, in the Rat Thrombosis Models", Japanese Journal of Pharmacology, (2000), 82 (Suppl. 1), 213P.	
	CN	JUST, M., et al., "A Comparison of a Specific Factor Xa Inhibitor (HMR-2906) and Recombinant Hirudin in a Dog Coronary Artery Thrombosis Model", XVIIth Congress of the International Society for Thrombosis and Haemostasis, Washington, D.C., (1999).	
	CO	CHU, V., et al., "Pharmacological Characterization of a Novel Factor Xa Inhibitor, FXV673", Thrombosis Research, (2001), Vol. 103, pp. 309-324.	
	CP	GUERTIN, K.R., et al., "Optimization of the β-Aminoester Class of Factor Xa Inhibitors. Part 2: Identification of FXV673 as a Potent and Selective Inhibitor with Excellent In Vivo Anticoagulant Activity", Bioorganic & Medicinal Chemistry Letters, (2002), Vol. 12, pp. 1671-1674.	
	CQ	RIES, U.J., et al., "Heterocyclic Coagulation Inhibitors: Design and Synthesis of Dual Direct Thrombin and Factor Xa Inhibitors", American Chemical Society - 226th National Meeting, (2003).	
	CR	PRUITT, JAMES R., et al., "Discovery of 1-(2-Aminomethylphenyl)-3-trifluoromethyl-N- [3-fluoro-2'-(aminosulfonyl)[1,1'-biphenyl)]-4-yl]-1 *H*-pyrazole-5-carboxyamide (DPC602), a Potent, Selective, and Orally Bioavailable Factor Xa Inhibitor", J. Med. Chem., (2003), Vol. 46, No. 25, pp. 5298-5315.	
	CS	NAGAHARA, T., et al., "Dibasic (Amidinoraryl)propanoic Acid Derivatives as Novel Blood Coagulation Factor Xa Inhibitors", J. Med. Chem., (1994), Vol. 37, No. 8, pp. 1200-1207.	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1]Applicant's unique citation designation number (optional). [2]Applicant is to place a check mark here if English language Translation is attached.

PTO/SB/08b (04-09)
Approved for use through 05/31/2009. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 3 of 4

Complete if Known	
Application Number	11/883,218-Conf. #9960
Filing Date	July 16, 2008
First Named Inventor	Frank Misselwitz
Art Unit	1615
Examiner Name	Not Yet Assigned
Attorney Docket Number	11987-00042-US

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s) , volume-issue number(s), publisher, city and/or country where published.	T[2]
	CT	MORISHIMA, Y., et al., "*In Vitro* Characteristics, Anticoagulant Effects and *In Vivo* Antithrombotic Efficacy of a Novel, Potent and Orally Active Direct Factor Xa Inhibitor, DU-176b", Blood, (2004), (Abst 1862).	
	CU	FUKUDA, T., et al., "Antithrombotic Properties of DU-176b, a Novel, Potent and Orally Active Direct Factor Xa Inhibitor in Rat Models of Arterial and Venous Thrombosis: Comparison with Fondaparinux, an Antithrombin Dependent Factor Xa Inhibitor", Blood, (2004), (Abst 1852).	
	CV	FURUGOHRI, T., et al, "Antithrombotic and Hemorrhagic Effects of DU-176b, a Novel, Potent and Orally Active Direct Factor Xa Inhibitor: A Wider Safety Margin Compared to Heparins and Warfarin", Blood, (2004), (Abst. 1851).	
	CW	Proteinase 2004: Strategies for New Medicines, 4th SCI-RSC Symposium, Proteinase Inhibitor Design, (2004).	
	CX	KOIZUMI, T. et al., "Effect of KFA-1982, a New Orally Active Factor Xa Inhibitor, in a Rabbit Venous Thrombosis Model", J. of Thrombosis and Haemostasis, Vol. 1, Suppl. 1, (2003), P2022. (abstract)	
	CY	NISHIDA, H., et al., "Synthesis and Evaluation of 1-Arylsulfonyl-3-piperazinone Derivatives as Factor Xa Inhibitors[1,2] III. Effect of Ring Opening of Piperazinone Moiety on Inhibition", Chem. Pharm. Bull, (2004), Vol. 52, No. 4. pp. 459-462.	
	CZ	NISHIDA, H., et al., "Synthesis and Evaluation of 1-Arylsulfonyl-3-piperazinone Derivatives as Factor Xa Inhibitors [1-3] IV. A Series of New Derivatives Containing a Spiro [5*H*-oxazolo[3,2-*a*]pyrazine-2(3*H*),4' -piperidin]-5-one Skeleton", Chem. Pharm. Bull., (2004), Vol. 52, No. 4, pp. 406-412.	
	CA1	NISHIDA, H., et al., "Synthesis and Evaluation of 1-Arylsulfonyl-3-piperazinone Derivatives as a Factor Xa Inhibitor[1,2] II. Substituent Effect on Biological Activities", Chem. Pharm. Bull., (2002), Vol. 50, No. 9, pp. 1187-1194.	
	CB1	NISHIDA, H., et al., "Synthesis and Evaluation of 1-Arylsulfonyl-3-piperazinone Derivatives as Factor Xa Inhibitor", Chem. Pharm. Bull. Vol. 49, No. 10, (2001), pp. 1237-1244.	
	CC1	YOUNG, S. C., "Factor Xa Inhibitor LY517717; A Novel and Effective Oral Anticoagulant", Medicinal Chemistry-12th RSC-SCI Symposium, 7-10 September 2003, Cambridge, UK;	
	CD1	M. Wiley, et al., 228th ACS National Meeting, Philadelphia, August 22-26, 2004, MEDI-252 & 254.	
	CE1	NISHIDA, H. et al., "Design Synthesis and Biological Activities of New Potent Factor Xa Inhibitor," 228th ACS National Meeting, Philadelphia, August 22-26, 2004, Slides from MED1-251.	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1]Applicant's unique citation designation number (optional). [2]Applicant is to place a check mark here if English language Translation is attached.

PTO/SB/08b (04-09)
Approved for use through 05/31/2009. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 4 of 4

Complete if Known	
Application Number	11/883,218-Conf. #9960
Filing Date	July 16, 2008
First Named Inventor	Frank Misselwitz
Art Unit	1615
Examiner Name	Not Yet Assigned
Attorney Docket Number	11987-00042-US

NON PATENT LITERATURE DOCUMENTS

Examiner Initials	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	CF1	Research and Development Pipeline, Yamanouchi Pharmaceutical Co. Ltd., Company World Wide Web site, "Yamanouchi and Fujisawa Enter Into a Basic Agreement to Merge on April 1, 2005", (2004), 7 pages.	
	CG1	NAZARÉ, M., et al., "Novel Factor Xa Inhibitors Based on a 2-Carboxyindole Scaffold: SAR of P4 Substituents in Combination With a Neutral P1 Ligand", Bioorganic & Medicinal Chemistry Letters, Vol. 14, (2004), pp. 4197-4201.	
	CH1	NAZARÉ, M., "Novel Factor Xa Inhibitors Based on a Benzoic Acid Scaffold and Incorporating a Neutral P1 Ligand", Bioorganic & Medicinal Chemistry Letters, Vol. 14, (2004), pp. 2801-2805.	
	CI1	CHOI-SLEDESKI, Y. M., et al., "Discovery of an Orally Efficacious Inhibitor of Coagulation Factor Xa Which Incorporates a Neutral P Ligand", Journal of Medicinal Chemistry, Vol. 46, No. 5, (2003), pp. 681-684.	
	CJ1	MAIGNAN, S., et al., "Molecular Structures of Human Factor Xa Complexed with Ketopiperazine Inhibitors: Preference for a Neutral Group in the S1 Pocket", Journal of Medicinal Chemistry, Vol. 46, No. 5, (2003), pp. 685-690.	
	CK1	ADLER, M., et al., "Crystal Structures of Two Potent Nonamidine Inhibitors Bound to Factor Xa", Biochemistry, Vol. 41, No. 52, (2002), pp. 15514-15523.	
	CL1	CHOU, Y.-L., et al., "Structure-Activity Relationships of Substituted Benzothiophene-Anthranilamide Factor Xa Inhibitors", Bioorganic & Medicinal Chemistry Letters, Vol. 13, (2003), pp. 507-511.	
	CM1	QUAN, M. L., et al., "Discovery of 1-(3'-Aminobenzisoxazol-5'-yl)-3-Trifluoromethyl-*N*-[2-Fluoro-4-[(2'-Dimethylaminomethyl)Imidazol-1-yl]Phenyl]-1*H*-Pyrazole-5-Carboxyamide Hydrochloride (Razaxaban), a Highly Potent, Selective, and Orally Bioavailable Factor Xa Inhibitor", Journal of Medicinal Chemistry, Vol. 48, No. 6, (2005), pp. 1729-1744.	
	CN1	PINTO, D. J.P., et al., "Discovery of 1-[3-(Aminomethyl)Phenyl]-*N*-[3-Fluoro-2'-(Methylsulfonyl)-[1,1'-Biphenyl]-4-yl]-3-(Trifluoromethyl)[1*H*-Pyrazole-5-Carboxamide (DPC423), a Highly Potent, Selective, and Orally Bioavailable Inhibitor of Blood Coagulation Factor Xa", Journal of Medicinal Chemistry, Vol. 44, No. 4, (2001), pp. 566-578.	
	CO1	HAGINOYA, N., et al., "Synthesis and Conformational Analysis of a Non-Amidine Factor Xa Inhibitor That Incorporates 5-Methyl-4,5,6,7-Tetrahydrothiazolo[5,4-*c*]Pyridine as S4 Binding Element", Journal of Medicinal Chemistry, Vol. 47, No. 21, (2004), pp. 5167-5182.	
	CP1	MEDERSKI, W., et al., "Halothiophene Benzimidazoles as P1 Surrogates of Inhibitors of Blood Coagulation Factor Xa", Bioorganic & Medicinal Chemistry Letters, Vol. 14, (2004), pp. 3763-3769.	
	CQ1	ZHANG, P., et al., "Design, Synthesis, and SAR of Anthranilamide-Based Factor Xa Inhibitors Incorporating Substituted Biphenyl P4 Motifs", Bioorganic & Medicinal Chemistry Letters, Vol. 14, (2004), pp. 983-987.	
	CR1	ZHANG, P., "Design, Synthesis, and SAR of Anthranilamide-based Factor Xa Inhibitors with Improved Functional Activity", Bioorganic & Medicinal Chemistry Letters, Vol.14, (2004), pp. 989-993.	
	CS1	WILLARDSEN, J. A., et al., "Design, Synthesis, and Biological Activity of Potent and Selective Inhibitors of Blood Coagulation Factor Xa", Journal of Medicinal Chemistry, Vol. 47, No. 16, (2004), pp. 4089-4099.	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1]Applicant's unique citation designation number (optional). [2]Applicant is to place a check mark here if English language Translation is attached.

685375_1

Electronic Acknowledgement Receipt

EFS ID:	5465038
Application Number:	11883218
International Application Number:	
Confirmation Number:	9960
Title of Invention:	Prevention and Treatment of Thromboembolic Disorders
First Named Inventor/Applicant Name:	Frank Misselwitz
Customer Number:	23416
Filer:	Christine Hansen/Sara Maloney
Filer Authorized By:	Christine Hansen
Attorney Docket Number:	BHC 051006
Receipt Date:	05-JUN-2009
Filing Date:	16-JUL-2008
Time Stamp:	16:17:34
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	IDS_Letter.pdf	35215 91877715893ba7b89e33ba16262eb5047ac75ee0	no	2

Warnings:	
Information:	

2	Information Disclosure Statement (IDS) Filed (SB/08)	IDS_Filed.pdf	213078 74bf12475bd67d1a5809306af352d4581e76cb60	no	4
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
3	NPL Documents	White.pdf	344761 a1e41608b07ba0a2630ecc9cdf7c7c0300610953	no	6
Warnings:					
Information:					
4	NPL Documents	Feign.pdf	1439147 103b8f8a18c841d401a544c4d40184ff366b1aa1	no	11
Warnings:					
Information:					
5	NPL Documents	Fang.pdf	451213 4ee833e2a00fb49316e4319b32cbe2f62bc3e468	no	7
Warnings:					
Information:					
6	NPL Documents	Raghaven.pdf	776079 28895825298c04bba559f9ec8c2560e26c950d38	no	15
Warnings:					
Information:					
7	NPL Documents	Wieland.pdf	596607 4eb511dc0d02531358866e2e927fc1cf4f274968	no	8
Warnings:					
Information:					
8	NPL Documents	Ries_28.pdf	992975 5884d5412554d1ea4d76c1675f645caac85da2bc	no	16
Warnings:					
Information:					
9	NPL Documents	Linkins.pdf	659960 e4a26beafd240215195a6c88cfb9b92e89691b76	no	17
Warnings:					
Information:					
10	NPL Documents	Goodman.pdf	313011 61297b50072f6979dc51113811df46a5d22acf95	no	10

Warnings:					
Information:					
11	NPL Documents	Rowland.pdf	912629 600cbdce2bba130deb3e498f1323ee9883cf028e	no	25
Warnings:					
Information:					
12	NPL Documents	Birkett.pdf	87014 3fac7713eb6982e1c0d881002f95a93a8dbebf1d	no	1
Warnings:					
Information:					
13	NPL Documents	Roehrig.pdf	139065 29facdc3d7f70882c2dea8d4fc156fd7ce9f9443	no	2
Warnings:					
Information:					
14	NPL Documents	Geerts.pdf	3638774 52b67bc349885eb3f96fcb5016caf85e6363699e	no	45
Warnings:					
Information:					
15	NPL Documents	Takehana.pdf	62855 bb2ecf8bce21e5c83efb997b32f0b51399bc8282	no	1
Warnings:					
Information:					
16	NPL Documents	Just.pdf	65540 c7d5c8089799fc2bc57e2b77e5233d8cecfe0e55	no	1
Warnings:					
Information:					
17	NPL Documents	Chu.pdf	892624 7760250e7fcbcf764bc369347c2cfbbd90acf731	no	16
Warnings:					
Information:					
18	NPL Documents	Guertin.pdf	212298 d6d7d957c9e8a142996408a828e7f9cff82d349a	no	4
Warnings:					
Information:					
19	NPL Documents	Ries.pdf	237959 db3fba97099f04d8c1fb87ef86d7076bc954566e	no	2

Warnings:					
Information:					
20	NPL Documents	Pruitt.pdf	1306439 49d970e8b823a2e5b8d558f0843b46367fc1a205	no	19
Warnings:					
Information:					
21	NPL Documents	Nahahara.pdf	663762 aa0ac005ce3a69bfc069b2330a5c966ecd33fd51	no	9
Warnings:					
Information:					
22	NPL Documents	Morishima.pdf	103331 ab0d0ba43a19381cb63ead711fe85e4778dc529d	no	1
Warnings:					
Information:					
23	NPL Documents	Fukuda.pdf	114121 f093d68781e99a3bc795f14bd1bfd3dd52323162	no	1
Warnings:					
Information:					
24	NPL Documents	Furugohri.pdf	109306 e98d5d01f7ba8434bc0b8bd72b6974024cba9a4d	no	1
Warnings:					
Information:					
25	NPL Documents	Proteinase.pdf	354018 5c532e96671f3ee7e1f2f38cc6465d6993e479a1	no	4
Warnings:					
Information:					
26	NPL Documents	Koizumi.pdf	41010 9286c5a142aeae39f5389397669d6872a8835357	no	2
Warnings:					
Information:					
27	NPL Documents	Nishida.pdf	260641 3eaa7e36404535e48a5cb449914bb317d15d0a31	no	4
Warnings:					
Information:					
28	NPL Documents	Nishida_406.pdf	455753 203865a9c2b9552a91733ea87036f291151dcff6	no	7

Warnings:					
Information:					
29	NPL Documents	Nishida_1187.pdf	620989 0bef9b52f9d009a59fc9a6ba86ea3b0db712b81a	no	8
Warnings:					
Information:					
30	NPL Documents	Nishida_1237.pdf	617503 0e5258955576c94135d705ddc9883ef2a321cf2b	no	8
Warnings:					
Information:					
31	NPL Documents	Young.pdf	21611 d4c90c4b80f72e414f014239d8fb06d54b71a876	no	1
Warnings:					
Information:					
32	NPL Documents	Wiley.pdf	880800 50ca8c81c1127a059f6bafb40ca4965d192ecc1c	no	4
Warnings:					
Information:					
33	NPL Documents	Nishida_251.pdf	6035886 f00ebb816afed742d1ec3955ad6d3ae34230bf17	no	16
Warnings:					
Information:					
34	NPL Documents	Research_Development.pdf	214645 0a7c8af55eb8584a9a80a8abca73c52ec736ecbd	no	7
Warnings:					
Information:					
35	NPL Documents	Nazare.pdf	263332 d82ae8bcc99aabfe9be5dc9606a3260fdd53ffb8	no	5
Warnings:					
Information:					
36	NPL Documents	Nazare_2805.pdf	226879 e279879fa5f13e2d3230a5875c65fe800c4d10c7	no	5
Warnings:					
Information:					
37	NPL Documents	Choi_Sledeski.pdf	350091 408f314274509034031b8bbcf219e51a8a8b161e	no	6

Warnings:					
Information:					
38	NPL Documents	Maignan.pdf	477200 0a9121cc22882f608d81ddfff4c91f7c45eac337	no	7
Warnings:					
Information:					
39	NPL Documents	Adler.pdf	947205 a30b859e63771ee1d67ea26f5c5e97da2ed2e39e	no	11
Warnings:					
Information:					
40	NPL Documents	Chou.pdf	297009 c323a2ffaa9d72fe256ff2087c87ec3ba27a46f1	no	5
Warnings:					
Information:					
41	NPL Documents	Quan.pdf	1247295 f0c0f76529e4caffeabdf587da13fe3b9574e73f	no	17
Warnings:					
Information:					
42	NPL Documents	Pinto.pdf	969889 cf3a34f6c8e97410541f3d15fe7aad30033b9ad0	no	15
Warnings:					
Information:					
43	NPL Documents	Haginoya.pdf	1410468 a6543ad9baf6e5677020061eadcd05c5f6826b73	no	17
Warnings:					
Information:					
44	NPL Documents	Mederski.pdf	280427 8b3561d50e7761861fd75a7484d5ff9d984a0c69	no	7
Warnings:					
Information:					
45	NPL Documents	Zhang.pdf	257514 49c675c65f05cdcd8f9fdda0d6bb25c6dba8eff0	no	5
Warnings:					
Information:					
46	NPL Documents	Zhang_993.pdf	227984 cb9287b7c6a7bfd22bdd92669c8a74bc625e30cd	no	5

Warnings:					
Information:					
47	NPL Documents	Willardsen.pdf	896299 5bb17b3ccdf65edcf242377f8f8a1cca22fdb614	no	12
Warnings:					
Information:					
			Total Files Size (in bytes):	31722211	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Docket No.: 11987-00042-US
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Frank Misselwitz et al.

Application No.: 11/883,218 Confirmation No.: 9960

Filed: July 16, 2008 Art Unit: 1615

For: PREVENTION AND TREATMENT OF THROMBOEMBOLIC DISORDERS Examiner: Not Yet Assigned

INFORMATION DISCLOSURE STATEMENT (IDS)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Madam:

Pursuant to 37 CFR 1.56, 1.97 and 1.98, the attention of the Patent and Trademark Office is hereby directed to the references listed on the attached PTO/SB/08. It is respectfully requested that the information be expressly considered during the prosecution of this application, and that the references be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

This Information Disclosure Statement is filed before the mailing date of a first Office Action on the merits as far as is known to the undersigned (37 CFR 1.97(b)(3)).

In accordance with 37 CFR 1.98(a)(2)(ii), Applicant has not submitted copies of U.S. patents and U.S. patent applications. Applicant submits herewith copies of foreign patents and non-patent literature in accordance with 37 CFR 1.98(a)(2).

The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 03-2775, under Order No. 11987-00042-US.

Dated: June 5, 2009

Respectfully submitted,

By Christine Hansen

Christine M. Hansen
Registration No.: 40,634
CONNOLLY BOVE LODGE & HUTZ LLP
1007 North Orange Street
P.O. Box 2207
Wilmington, Delaware 19899
(302) 658-9141
(302) 658-5614 (Fax)
Attorney for Applicant

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
11/883,218	07/16/2008	Frank Misselwitz	BHC 051006

CONFIRMATION NO. 9960

23416
CONNOLLY BOVE LODGE & HUTZ, LLP
P O BOX 2207
WILMINGTON, DE 19899

PUBLICATION NOTICE

Title: Prevention and Treatment of Thromboembolic Disorders

Publication No.US-2009-0004265-A1
Publication Date:01/01/2009

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Office of Public Records. The Office of Public Records can be reached by telephone at (703) 308-9726 or (800) 972-6382, by facsimile at (703) 305-8759, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently http://pair.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

Docket No.: 11987-00042-US
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Witz Missel et al.

Application No.: 11/883,218 | Confirmation No.: 9960

Filed: July 27, 2008 | Art Unit: 1614

For: PREVENTION AND TREATMENT OF THROMBOEMBOLIC DISORDERS | Examiner: Not Yet Assigned

INFORMATION DISCLOSURE STATEMENT (IDS)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Pursuant to 37 CFR 1.56, 1.97 and 1.98, the attention of the Patent and Trademark Office is hereby directed to the references listed on the attached PTO/SB/08. It is respectfully requested that the information be expressly considered during the prosecution of this application, and that the references be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

This Information Disclosure Statement is filed before the mailing date of a first Office Action on the merits as far as is known to the undersigned (37 CFR 1.97(b)(3)).

In accordance with 37 CFR 1.98(a)(2)(ii), Applicant has not submitted copies of U.S. patents and U.S. patent applications. Applicant submits herewith copies of foreign patents and non-patent literature in accordance with 37 CFR 1.98(a)(2).

The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith to our Deposit Account No. 03-2775, under Order No. 11987-00042-US.

630813_1

The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith to our Deposit Account No. 03-2775, under Order No. 11987-00042-US.

Dated: October 22, 2008

Respectfully submitted,

By Christine Hansen

Christine M. Hansen
Registration No.: 40,634
CONNOLLY BOVE LODGE & HUTZ LLP
1007 North Orange Street
P.O. Box 2207
Wilmington, Delaware 19899
(302) 658-9141
(302) 658-5614 (Fax)
Attorney for Applicant

PTO/SB/08b (08-08)
Approved for use through 08/31/2008. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 10

Complete if Known	
Application Number	11/883,218-Conf. #9960
Filing Date	July 27, 2008
First Named Inventor	Witz Missel
Art Unit	N/A
Examiner Name	Not Yet Assigned
Attorney Docket Number	11987-00042-US

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	AA*	US-2,811,555	10-29-1957	Larive, et al.	
	AB*	US-3,279,880	10-18-1966	Straley et al.	
	AC*	US-4,250,318	02-10-1981	Dostert et al.	
	AD*	US-4,128,654	12-05-1978	Fugitt et al.	
	AE*	US-4,327,725	05-04-1982	Cortese et al.	
	AF*	US-4,500,519	02-19-1985	Lormeau, et al.	
	AG*	US-4,705,779	11-10-1987	Madi-Szabo, et al.	
	AH*	US-4,765,989	08-23-1988	Wong et al.	
	AI*	US-4,948,801	08-14-1990	Carlson et al.	
	AJ*	US-4,977,173	12-11-1990	Brittelli et al.	
	AK*	US-5,002,937	03-26-1991	Bosies et al.	
	AL*	US-5,254,577	10-19-1993	Carlson, et al.	
	AM*	US-5,349,045	09-20-1994	Ying Jiang	
	AN*	US-5,532,255	07-02-1996	Raddatz et al.	
	AO*	US-5,561,148	10-01-1996	Gante et al.	
	AP*	US-5,565,571	10-01-1996	Barbachyn et al.	
	AQ*	US-5,654,428	08-05-1997	Barbachyn et al.	
	AR*	US-5,654,435	08-05-1997	Barbachyn et al.	
	AS*	US-5,688,792	11-18-1997	Barbachyn, et al.	
	AT*	US-5,756,732	05-26-1998	Barbachyn et al.	
	AU*	US-5,792,765	08-11-1998	Riedl, et al.	
	AV*	US-5,801,246	09-01-1998	Barbachyn et al.	
	AW*	US-5,827,857	10-27-1998	Riedl, et al.	
	AX*	US-5,910,504	06-08-1999	Hutchinson, et al.	
	AY*	US-5,922,708	07-13-1999	Riedl, et al.	
	AZ*	US-5,929,248	07-27-1999	Barbachyn et al.	
	AA1*	US-5,935,724	08-10-1999	Spillman et al.	
	AB1*	US-5,972,947	10-26-1999	Tsaklakidis et al.	
	AC1*	US-5,977,373	11-02-1999	Gadwood et al.	
	AD1*	US-5,998,406	12-07-1999	Hester et al.	
	AE1*	US-6,069,160	05-30-2000	Stolle, et al.	
	AF1*	US-6,159,997	12-12-2000	Tsujita et al.	
	AG1*	US-6,218,413	04-17-2001	Hester et al.	
	AH1*	US-6,251,869	06-26-2001	Michael J. Bohanon	
	AI1*	US-6,265,178	07-24-2001	Martin, Jr.	
	AJ1*	US-6,281,210	08-28-2001	Hester, Jr.	
	AK1*	US-6,294,201-B1	09-25-2001	Kettelhoit et al	
	AL1*	US-2001/0029351-A1	10-11-2001	Falotico et al.	
	AM1*	US-2001/0046987-A1	11-29-2001	Hester et al.	
	AN1*	US-2003/0161882-A1	08-28-2003	Waterman	
	AO1*	US-2004/0162427-A1	08-19-2004	Rosentreter et al.	
	AP1*	US-6,805,881-B1	10-19-2004	Kanikanti et al.	
	AQ1*	US-6,818,243-B2	11-16-2004	Nagashima et al.	
	AR1*	US-2004/0242660-A1	12-02-2004	Straub et al.	
	AS1*	US-2005/0064006-A1	03-24-2005	Perzborn et al.	
	AT1*	US-2005/0182055-A1	08-18-2005	Berwe et al.	

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 10

Complete if Known	
Application Number	11/883,218-Conf. #9960
Filing Date	July 27, 2008
First Named Inventor	Witz Missel
Art Unit	N/A
Examiner Name	Not Yet Assigned
Attorney Docket Number	11987-00042-US

	AU1*	US-2005/0261502-A1	11-24-2005	Straub et al.	
	AV1*	US-7,034,017-B2	04-25-2006	Straub et al.	
	AW1*	US-7,045,631-B2	04-25-2006	Straub et al.	
	AX1*	US-2006/0154969-A1	07-13-2006	Rosentreter et al.	
	AY1*	US-7,078,417-B2	07-18-2006	Rosentreter et al.	
	AZ1*	US-7,109,218-B2	09-19-2006	Rosentreter et al.	
	AA2*	US-7,129,255-B2	10-31-2006	Rosentreter et al.	
	AB2*	US-2006/0258724-A1	11-16-2006	Straub et al.	
	AC2*	US-2007/0026065-A1	02-01-2007	Benke et al.	
	AD2*	US-2007/0149522-A1	06-28-2007	Thomas	
	AE2*	US-2008/0026057-A1	01-31-2008	Benke	
	AF2*	US-2008/0090815-A1	04-17-2008	Straub et al.	
	AG2*	US-2008/0200674-A1	08-21-2008	Straub et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document: Country Code[3]-Number[4]-Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	BA	DE-2836305-A1	03-01-1979	Delalande SA		See US 4250318
	BB	GB-2140687	12-05-1984	Alza Corp.		
	BC	EP-0 127 902 A2	12-12-1984	E.I. Du Pont de Nemours and Co.		See US 4705799
	BD	EP-0 316 594 A1	05-24-1989	The Du Pont Merck Pharmaceutical Co.		See US 4977173
	BE	EP-0350002-A1	01-10-1990	Boehringer Mannheim GmbH		See US 5002937
	BF	EP-0 352 781 A2	01-31-1990	E.I. Du Pont De Nemours and Co.		See US 4948801
	BG	WO-93/09103 A1	05-13-1993	The Upjohn Company		See US 5565571
	BH	WO-93/23384-A1	11-25-1993	The UpJohn Company		
	BI	EP-0623615-A1	11-09-1994	Merck Patent GmbH		See US 5532255
	BJ	EP-0645376 A1	03-29-1995	Merck Patent GmbH		See US 5561148
	BK	EP-0738726-A1	10-23-1996	Bayer AG		See US 6069160
	BL	WO-97/03072-A1	01-31-1997	Boehringer Mannheim GmbH		See US 5972947
	BM	WO-97/09328 A1	03-13-1997	Pharmacia & Upjohn Company		See US 5935724
	BN	WO-97/10223-A1	03-20-1997	Pharmacia & UpJohn Company		
	BO	EP-0 785 200 A2	07-23-1997	Bayer AG		See US 5827857
	BP	DE-196 04 223 A1	08-07-1997	Bayer AG		See US 5792765
	BQ	WO-98/01446-A1	01-15-1998	Zeneca Limited		
	BR	WO-98/54161 A1	12-03-1998	Pharmacia & Upjohn Company		See US 6218413
	BS	WO-99/02525 A1	01-21-1999	Pharmacia & Upjohn Company		See US 5977373
	BT	WO-99/03846 A1	01-28-1999	Bayer Aktiengesellschaft		See Abstract
	BU	WO-99/21535-A1	05-06-1999	Bayer Aktiengesellschaft		See US 6294201 B1
	BV	WO-99/24428 A1	05-20-1999	Pharmacia & Upjohn Company		See US 5998406
	BW	WO-99/29688 A1	06-17-1999	Pharmacia & Upjohn Company		See US 6265178
	BX	WO-99/31092-A1	06-24-1999	Merck Patent GmbH		See Abstract

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 3 of 10

Complete if Known	
Application Number	11/883,218-Conf. #9960
Filing Date	July 27, 2008
First Named Inventor	Witz Missel
Art Unit	N/A
Examiner Name	Not Yet Assigned
Attorney Docket Number	11987-00042-US

	BY	EP-0930076-A1	07-21-1999	Sankyo Company Limited		
	BZ	WO-99/37304-A1	07-29-1999	Rhone-Poulenc Rorer Pharmaceuticals		
	BA1	WO-99/37630-A1	07-29-1999	Versicor, Inc.		
	BB1	WO-99/40094-A1	08-12-1999	Bayer Aktiengesellschaft		See Abstract
	BC1	EP-0950386-A2	10-20-1999	Cordis Corporation		
	BD1	WO-99/59616-A1	11-25-1999	Pharmacia & UpJohn Company		
	BE1	WO-00/16748-A1	03-30-2000	Bayer AG		See US 6805881 B1
	BF1	WO-01/42242-A1	06-14-2001	Ortho-McNeil Pharmaceutical, Inc.		
	BG1	WO-01/44212-A1	06-21-2001	Pharmacia & UpJohn Company		See US 6281210 B2
	BH1	WO-01/46185-A1	06-28-2001	Pharmacia & UpJohn Company		See US 2001/0046987 A1
	BI1	WO-01-47949-A1	07-05-2001	Ajinomoto Co., Inc.		See US 6818243 B2
	BJ1	DE-19962924-A1	07-05-2001	Bayer AG		See US 7157456 B2
	BK1	AU-744002	02-14-2002	Merck Patent GmbH		
	BL1	WO-02/25210-A1	03-28-2002	Sht Co., Ltd.		
	BM1	DE-10105989-A1	08-14-2002	Bayer AG		See US 7034017 B2
	BN1	WO-02/064575-A1	08-22-2002	Bayer AG		See US 7034017 B2
	BO1	WO-02/070520-A1	09-12-2002	Bayer Aktiengesellschaft		See US 2004/0162427 A1
	BP1	WO-02/070484-A1	09-12-2002	Bayer Aktiengesellschaft		See US 2005/0261502 A1
	BQ1	WO-02/070485-A1	09-12-2002	Bayer Aktiengesellschaft		See US 2006/0154969 A1
	BR1	WO-02/079195-A1	10-10-2002	Bayer Aktiengesellschaft		See US 7,078,417 B2
	BS1	WO-02/079196-A1	10-10-2002	Bayer Aktiengesellschaft		See US 7,129,255 B2
	BT1	DE-10129725-A1	01-02-2003	Bayer AG		See US 2004/242660 A1
	BU1	WO-03/000256-A1	01-03-2003	Bayer HealthCare AG		See US 2004/242660 A1
	BV1	WO-03/08384-A1	01-30-2003	Bayer Aktiengesellschaft		See US 7,045,631 B2
	BW1	WO-03/035133-A1	05-01-2003	Bayer HealthCare AG et al.		See US 2005/064006 A1
	BX1	WO-03/053441-A1	07-03-2003	Bayer Aktiengesellschaft		See US 7,109,218 B2
	BY1	WO-2004/060887-A1	07-22-2004	Bayer HealthCare AG et al.		See US 2007/149522 A1
	BZ1	WO-2005/060940-A1	05-07-2005	Bayer HealthCare AG et al.		See US 2008/026057 A1
	BA2	DE-10355461-A1	06-23-2005	Bayer HealthCare AG et al.		See US 2008/026057 A1
	BB2	WO-2006/072367-A1	07-13-2006	Bayer HealthCare AG et al.		See US 2007/026065 A1
	BC2	WO-2005/068456-A1	07-28-2005	Bayer HealthCare AG et al.		See US 7351823 B2

PTO/SB/08b (08-08)
Approved for use through 08/31/2008. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 4 of 10

Complete if Known	
Application Number	11/883,218-Conf. #9960
Filing Date	July 27, 2008
First Named Inventor	Witz Missel
Art Unit	N/A
Examiner Name	Not Yet Assigned
Attorney Docket Number	11987-00042-US

	BD2	WO-2006/079474-A1	08-03-2006	Bayer HealthCare AG et al.		
	BE2	WO-2007/036306-A1	04-05-2007	Bayer HealthCare AG et al.		See Abstract
	BF2	WO-2007/039134-A1	04-12-2007	Bayer HealthCare AG et al.		See Abstract
	BG2	WO-2007/039132-A1	04-12-2007	Bayer HealthCare AG et al.		See Abstract
	BH2	WO-2007/039122-A2	04-12-2007	Bayer HealthCare AG et al.		See Abstract
	BI2	WO-2007/042146-A1	04-19-2007	Bayer HealthCare AG et al.		See Abstract
	BJ2	WO-2008/012002-A1	01-31-2008	Bayer HealthCare AG et al.		See Abstract
	BK2	WO-2008/052671-A1	05-08-2008	Bayer HealthCare AG et al.		See Abstract

BM2

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. * CITE NO.: Those application(s) which are marked with an single asterisk (*) next to the Cite No. are not supplied (under 37 CFR 1.98(a)(2)(iii)) because that application was filed after June 30, 2003 or is available in the IFW. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

PTO/SB/08b (08-08)
Approved for use through 08/31/2008. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet	5	of	10

Complete if Known	
Application Number	11/883,218-Conf. #9960
Filing Date	July 27, 2008
First Named Inventor	Witz Missel
Art Unit	N/A
Examiner Name	Not Yet Assigned
Attorney Docket Number	11987-00042-US

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	CA	BONO, F., et al., "Human Umbilical Vein Endothelial Cells Express High Affinity Receptors for Factor Xa", Journal of Cellular Physiology, 1997, Vol. 172, pp. 36-43.	
	CB	COCKS, T. M., et al., "Protease-Activated Receptors: Sentries for Inflammation", Tips, 2000, Vol. 21, pp. 103-108.	
	CC	ROSS, R., "Atherosclerosis- An Inflammatory Disease", New England J. of Medicine, 1999, Vol. 340, No. 2, pp. 115-126.	
	CD	NAKATA, M., et al., "DX9065a an Xa Inhibitor, Inhibits Prothrombin-Induced A549 Lung Adenocarcinoma Cell Proliferation", Cancer Letters, 1998, Vol. 122, pp. 127-133.	
	CE	KAISER, B., et al., "A Synthetic Inhibitor of Factor Xa, DX-9065a, Reduces Proliferation of Vascular Smooth Muscle Cells in Vivo in Rats", Thrombosis Research, 2000, Vol. 98, pp. 175-185.	
	CF	ALTIERI, D. C., et al., "Identification of Effector Cell Protease Receptor-1", The Journal of Immunology, 1990, Vol. 145, No. 1, pp. 246-253.	
	CG	COUGHLIN, S. R., "Thrombin Signalling and Protease-Activated Receptors", Nature, 2000, Vol. 407, pp. 258-264.	
	CH	ORNSTEIN, D. L., et al., "Cancer, Thrombosis, and Anticoagulants", Current Opinion in Pulmonary Medicine, 2000, Vol. 6, pp. 301-308.	
	CI	DABBAGH, K., et al., "Thrombin Stimulates Smooth Muscle Cell Procollagen Synthesis and mRNA Levels via a PAR-1 Mediated Mechanism", Thrombasis and Haemostasis, vol. 79, no.2 1997, pp. 405-409.	
	CJ	HERAULT, J-P., et al., "Activation of Human Vascular Endothelial Cells by Factor Xa: Effect of Specific Inhibitors", Biochemical Pharmacology, 1999, Vol. 57, pp. 603-610.	
	CK	LEVEUGLE, B., et al., "Heparin Oligosaccharides that Pass the Blood- Brain Barrier Inhibit β-Amyloid Precursor Protein Secretion and Heparin Binding to β-Amyloid Peptide", Journal of Neurochemistry, 1998, Vol. 70, No. 2, pp. 736-744.	
	CL	MOLINO, M., et al., "Differential Expression of Functional Protease-Activated Receptor-2 (PAR-2) in Human Vascular Smooth Muscle Cells", Arteriosclerosis, Thrombasis, and Vascular Biology, vol. 18, no. 5, 1998, pp. 825-832.	
	CM	PLESCIA, J., et al., "Activation of MAC-1 (CD11b/CD18)-Bound Factor X by Release Cathepsin G Defines an Alternative Pathway of Leucocyte Initiation of Coagulation", Biochem. J., 1996, Vol. 319, pp. 873-879.	
	CN	HOWELLS, G. L., et al., "Proteinase-Activated Receptor-2: Expression by Human Neutrophils", Journal of Cell Science, 1997, Vol. 110, pp. 881-887.	
	CO	HERBERT, J.-M., et al., "Effector Protease Receptor 1 Mediates the Mitogenic Activity of Factor Xa for Vascular Smooth Muscle Cells in Vitro and In Vivo", J. Clin. Invest., 1998, Vol. 101, no. 5, pp. 993-1000.	
	CP	DONNELLY, K. M., et al., "*Ancylostoma caninum* Anticoagulant Peptide Blocks Metastasis In Vivo and Inhibits Factor Xa Binding to Melanoma Cells In Vitro", Thromb Haemost, 1998, Vol. 79, pp. 1041-1047.	
	CQ	RAGOSTA, M., et al., "Specific Factor Xa Inhibition Reduces Restenosis After Balloon Angioplasty of Atherosclerotic Femoral Arteries in Rabbits", Circulation, 1994, Vol. 89, No. 3, pp. 1262-1271.	
	CR	ZHANG, Y., et al., "Tissue Factor Controls the Balance of Angiogenic and Antiangiogenic Properties of Tumor Cells in Mice", J. Clin. Invest., 1994, Vol. 94, pp. 1320-1327.	

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 6 of 10

Complete if Known	
Application Number	11/883,218-Conf. #9960
Filing Date	July 27, 2008
First Named Inventor	Witz Missel
Art Unit	N/A
Examiner Name	Not Yet Assigned
Attorney Docket Number	11987-00042-US

	CS	GREEN, D., et al., "Lower Mortality in Cancer Patients Treated with Low-Molecular-Weight Versus Standard Heparin", The Lancet, 1992, Vol. 339, p. 1476.	
	CT	KO, F. N., et al., "Coagulation Factor Xa Stimulates Platelet-Derived Growth Factor Release and Mitogenesis in Cultured Vascular Smooth Muscle Cells of Rat", J. Clin. Invest., 1996, Vol. 98, No. 6, pp. 1493-1501.	
	CU	KAKKAR, A. K., et al., "Antithrombotic Therapy in Cancer", BMJ, 1999, Vol. 3318, pp. 1571-1572.	
	CV	GASIC, G. P., et al., "Coagulation Factors X, Xa, and Protein S as Potent Mitogens of Cultured Aortic Smooth Muscle Cells", Proc. Natl. Acad. Sci. USA, 1992, Vol. 89, pp. 2317-2320.	
	CW	CIRINO, G., et al., "Factor Xa as an Interface Between Coagulation and Inflammation: Molecular Mimicry of Factor Xa Association with Effector Cell Protease Receptor-1 Induces Acute Inflammation In Vivo", J. Clin. Invest., 1997, Vol. 99, No. 10, pp. 2446-2451.	
	CX	SENDEN, N. H. M., et al., "Factor Xa Induces Cytokine Production and Expression of Adhesion Molecules by Human Umbilical Vein Endothelial Cells", The Journal of Immunology, 1998, Vol. 161, pp. 4318-4324.	
	CY	PAPAPETROPOULOS, A., et al., "Hypotension and Inflammatory Cytokine Gene Expression Triggered by Factor Xa-Nitric Oxide Signaling", Proc. Natl. Acad. Sci. USA, 1998, Vol. 95, pp. 4738-4742.	
	CZ	CAMERER, E., et al., "Tissue Factor- and Factor X-dependent Activation of Protease-Activated Receptor 2 by Factor VIIa", PNAS, 2000, Vol. 97, No. 10, pp. 5255-5260.	
	CA1	DONOVAN, F. M., et al., "Thrombin Induces Apoptosis in Cultured Neurons and Astrocytes via a Pathway Requiring Tyrosine Kinase and RhaA Activities", The Journal of Neuroscience, 1997, Vol. 17, No. 14, pp. 5316-5326.	
	CB1	LINDNER, J. R., et al., "Delayed Onset of Inflammation in Protease-Activated Receptor-2-Deficient Mice", The Journal of Immunology, 2000, pp. 6504-6510.	
	CC1	BOUCHARD, B. A., et al., "Effector Cell Protease Receptor-1, a Platelet Activation-dependent Membrane Protein, Regulates Prothrombinase-catalyzed Thrombin Generation", The Journal of Biological Chemistry, 1997, Vol. 272, No. 14, pp. 9244-9251.	
	CD1	MOLINO, M., et al., "Endothelial Cell Thrombin Receptors and PAR-2", The Journal of Biological Chemistry, 1997, Vol. 272, No. 17, pp. 11133-11141.	
	CE1	NICHOLSON, A. C., et al., "Effector Cell Protease Receptor-1 Is a Vascular Receptor for Coagulation Factor Xa", The Journal of Biological Chemistry, 1996, Vol. 271, No. 45, pp. 28407-28413.	
	CF1	WATSON, D. J., et al., "Heparin-Binding Properties of the Amyloidogenic Peptides Aβ and Amylin", The Journal of Biological Chemistry, 1997, Vol. 272, No. 50, pp. 31617-31624.	
	CG1	TUSZYNSKI, G. P., et al., "Isolation and Characterization of Antistasin", The Journal of Biological Chemistry, 1987, Vol. 262, No. 20, pp. 9718-9723.	
	CH1	KRANZHÖFER, R., et al., "Thrombin Potently Stimulates Cytokine Production in Human Vascular Smooth Muscle Cells but Not in Mononuclear Phagocytes", Circulation Research, 1996, Vol. 79, No. 2, pp. 286-294.	
	CI1	SCHWARTZ, R. S., et al., "Neointimal Thickening After Severe Coronary Artery Injury is Limited by Short-term Administration of a Factor Xa Inhibitor", Circulation, 1996, Vol. 93, No. 8, pp. 1542-1548.	
	CJ1	ABENDSCHEIN, D. R., et al., "Inhibition of Thrombin Attenuates Stenosis After Arterial Injury in Minipigs", JACC, 1996, Vol. 28, No. 7, pp. 1849-1855.	
	CK1	CARMELIET, P., et al., "Gene Manipulation and Transfer of the Plasinogen and Coagulation System in Mice", Seminars in Thrombosis and Hemostasis, 1996, Vol. 22, No. 6, pp. 525-542.	
	CL1	STOUFFER, G. A., et al., "The Role of Secondary Growth Factor Production in Thrombin-Induced Proliferation of Vascular Smooth Muscle Cells", Seminars in Thrombosis and	

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 7 of 10

Complete if Known	
Application Number	11/883,218-Conf. #9960
Filing Date	July 27, 2008
First Named Inventor	Witz Missel
Art Unit	N/A
Examiner Name	Not Yet Assigned
Attorney Docket Number	11987-00042-US

		Hemostasis, 1998, Vol. 24, No. 2, pp. 145-150.	
	CM1	BEVILACQUA, M. P., et al., "Inducible Endothelial Functions in Inflammation and Coagulation", Seminars in Thrombosis and Hemostasis, 1987, Vol. 13, No. 4, pp. 425-433.	
	CN1	RIEDL, B., et al., "Recent Developments with Oxazolidinone Antibiotics", Exp. Opin. Ther. Patents, 1999, Vol. 9, No. 5, pp. 625-633.	
	CO1	BARBACHYN, M.R., et al., "Identification of Novel Oxazolidinone (U-100480) with Potent Antimycobacterial Activity", J. Med. Chem., 1996, Vol. 39, pp. 680-685.	
	CP1	TUCKER, J. A., et al, "Piperazinyl Oxazolidinone Antibacterial Agents Containing a Pyridine, Diazene, or Triazene Heteroaromatic Ring", J. Med. Chem. 1998, Vol. 41, pp. 3727-3735.	
	CQ1	BRICKNER, S.J., et al., "Synthesis and Antibacterial Activity of U-100592 and U-100766, Two Oxazolidinone Antibacterial Agents for the Potenial treatment of Multidrug-Resistant Gram-Positive Bacterial Infections" J. Med. Chem., 1996, Vol. 39, pp. 673-679	
	CR1	GREGORY, W.A., et al., "Antibacterials. Synthesis and Structure-Activity Studies of 3-Aryl-2-oxooxazolidines. 1. The "B" Group", J. Med. Chem., 1989, Vol. 32, No. 8, pp. 1673-1681.	
	CS1	BERRY, C. N., et al., "Antithrombotic Actions of Argatroban in Rat Models of Venous, 'Mixed' and Arterial Thrombosis, and its Effects on the Tail Transection Bleeding Time", Br. J. Pharmacol., 1994, Vol. 113, pp. 1209-1214.	
	CT1	MENG, K., et al., "Effect of Acetylsalicyclic Acid of Experimentally Induced Arterial Thrombosis in Rats", Naunyn-Schmiedeberg's Arch. Pharmacol.,1977, Vol. 301, pp. 115-119.	
	CU1	CHERN, J.W., et al., "Studies on Quinazolines IX:[1] Fluorination Versus 1,2-Migration on the Reaction of 1,3-Bifunctionalized Amino-2-Propanol with DAST", Tetrahedron Lett., 1998, Vol. 39, pp. 8483-8486.	
	CV1	SHAKESPEARE, W. C., et al., "Palladium-Catalyzed Coupling of Lactams with Bromobenzenes", Tetrahedron Lett., 1999, Vol. 40, pp. 2035*2038.	
	CW1	RENGER, B., et al., "Direkte *N*-Arylierung von Amiden: Eine Verbesserung der Goldberg-Reaktion", Synthesis, 1985, pp. 856-860.	
	CX1	AEBISCHER, E., et al., "Synthesis of *N*-Arylrolipram Derivatives - Potent and Selective Phosphodiesterase-IV Inhibitors - by Copper Catalyzed Lactam-Aryl Halide Coupling", Hetercycles, 1998, Vol. 48, No. 11 , pp. 2225-2229.	
	CY1	PFEIL, E., et al., "β-Aminoäthylierung von Indol und 2-methylindol", Angew Chem., 1967, Vol. 79, No. 4, pp. 188-189.	
	CZ1	ZIEGLER, C. B., et al., "Synthesis of Some Novel 7-Substituted Quinolonecarboxylic Acids *via* Nitroso and Nitrone Cycloadditions", J. Hetercycl. Chem., 1988, Vol. 25, No. 2, pp. 719-723.	
	CA2	BARTOLI, G., et al, "Electronic and Steric Effects in Nucleophilic Aromatic Substitution. Reaction by Phenoxides as Nucleophiles in Dimethyl Sulfoxide", J. Org. Chem., 1975, Vol. 40, No. 7, pp. 872-874.	
	CB2	REPPE, et al., "*N-p-Merthoxyphenyl-pyrrolidon*", Justus Liebigs Ann. Chem., 1955 Vol. 596, p. 208.	
	CC2	LUVALLE, J.E., et al., "Oxidation Processes. XXI.[1] The Autoxidation of the ρ-Phenylenediamines", J. Am. Chem. Soc., 1948, Vol. 70, pp. 2223-2233.	
	CD2	SNYDER, H.R., et al., "Imidazo[4,5*f*]quinolines III: Antibacterial 7-Methyl-9-(substituted Arylamino)imidazo[4,5-*f*]quinolines", J. Pharm. Sci., 1977, Vol. 66, pp. 1204-1406.	
	CE2	ADAMS, R., et al., "Sulfanilamide Derivatives. I", J. Am. Chem. Soc. 1939, Vol. 61, pp. 2342-2349.	
	CF2	KHANNA, I.K. , et al., "1,2-Diarylpyrroles as Potent and Selective Inhibitors of Cyclooxygenase-2", J. Med. Chem., 1997, Vol. 40 , pp. 1619-1633.	
	CG2	GUTCAIT, A., et al., "Studies on Quinazolines. 6.[1] Asymmetric Synthesis of (S)-(+)- and (R)-(-)-3-[[4-(2-Methoxyphenyl)piperazin-1-yl]methylthio-2,3,-dihydromidazo[1,2-c]quinazolines",	

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 8 of 10

Complete if Known	
Application Number	11/883,218-Conf. #9960
Filing Date	July 27, 2008
First Named Inventor	Witz Missel
Art Unit	N/A
Examiner Name	Not Yet Assigned
Attorney Docket Number	11987-00042-US

		Tetrahedron Asym., 1996, Vol. 7, No. 6, pp. 1641-1648.	
	CH2	GRELL, W., et al., "Repaglinide and Related Hypoglycemic Benzoic Acid Derivatives", J. Med. Chem., 1998, Vol. 41, pp. 5219-5246.	
	CI2	ARTICO, M. et al., "Rsearch on Compounds with Antiblastic Activity", Farmaco Ed. Sci. 1969, Vol. 24, pp. 179-190.	
	CJ2	DANKWARDT, S. M., et al., "Nonpeptide Bradykinin Antagonist Analogs based on a Model of a Sterling-Winthrop Nonpeptide Bradykinin Antagonist Overlapped with Cyclic Hexapeptide Bradykinin Antagonist Peptides", Bioorg. Med. Chem. Lett., 1997, Vol. 7, No. 14, pp. 1921-1926.	
	CK2	REPPE, et al., "*N-6-Aminohexyl-pyrrolidon*", Justus Liebigs Ann. Chem. 1955, Vol. 596, pp. 204.	
	CL2	BOUCHET, P., et al., "σ Values of *N*-Substitutes Azoles", J. Chem. Soc. Perkin Trans., 1974, Vol. 2, pp. 449-451.	
	CM2	SURREY, A. R., et al., "The Preparation of N-Benzyl-3-Morpholones and N-Benzyl-3-Homomorpholones from N-(Hydroxyalkyl)-chloroacetamides" J. Amer. Chem. Soc., 1955, Vol. 77, pp. 633-636.	
	CN2	TONG, L.K.J., et al., "The Mechanism of Dye Formation in Color Photography. VII. Intermediate Bases in the Deamination of Quinonediimines" J. Amer. Chem. Soc. 1960, Vol. 82, 1988-2001.	
	CO2	DELANDE, S.A., "Heterocycles", Chemical Abstracts, American Chemical Society, 1979, Vol. 90, pp. 663.	
	CP2	BOTS, M., et al., Coagulation and Fibrinolysis Markers and Risk of Dementia," Haemostasis, Vol. 28 (1998); pp. 216-222.	
	CQ2	BENZAKOUR, O., et al., "Cellular and molecular events in atherogenesis; basis for pharmocological and gene therapy approaches to stenosis," Cellular Pharmacology, 1996, Vol 3, pp. 7-22.	
	CR2	KANTHOU, C., et al., "Cellular effects of thrombin and their signalling pathways," Cellular Pharmacology, Vol. 2 (1995); pp. 293-302.	
	CS2	KAISER, B., et al., "Antiproliferation Action of Factor Xa Inhibitors in a Rat Model of Chronic Restenosis," Abstracts of the XVIIth Congress of the International Society on Thrombosis and Haemostasis, August 1999, p. 144.	
	CT2	TYRRELL, D., et al., "Heparin in Inflammation: Potential Therapeutic Applications Beyond Anticoagulation," Advances in Pharmacology, Vol. 46 (1999); pp. 151-208.	
	CU2	SMIROVA, I., et al., "Thrombin Is an Extracellular Signal that Activates Intracellular Death Protease Pathways Inducing Apoptosis in Model Motor Neurons," J. Neurobiology, Vol. 36 (1998); pp. 64-80.	
	CV2	BONO, F., et al., "Factor Xa Activates Endothelial Cells by a Receptor Cascade Between EPR-1 and PAR-2," Arterioscler Thromb Vasc Biol., Nov. 2000; pp 1-6.	
	CW2	LALA, P. et al, "Role of Nitric Oxide in tumor progression: Lessons Learned from Experimental Tumors," Cancer and Metastasis Review," Vol. 17, pages 91-106 (1998).	
	CX2	GOLUB, T., et al., "Molecular Classification of Cancer Science (1999), Vol. 286, 531-537.	
	CY2	FDA mulls drug to slow late-stage Alzheimer's [online], [retrieved on 2003-09-23]. Retrieved from the internet, URL:http://www.cnn.com/2003/HEALTH/conditions/09/24/alzheimers.drug.ap/index.html>.	
	CZ2	Ullman's Encyclopedia of Industrial Chemistry, Fifth Revised Ed., Editors: Elvers, B., Hawkins, S., VCH Verlagsgesellschaft mbH, Weinheim, 19985-1996, Ch. 5, 488-506.	
	CA3	ZHU, B., Scarborough, R., "Recent Advances in Inhibitors of Factor Xa in the Prothrombinase Complex," *Curr. Opinions Card. Pul. Ren. Inv. Drugs,* 1:63-87 (1999).	
	CB3	UZAN, A., "Antithrombotic Agents," *Emerging Drugs: The Prospect for Improved Medicines,"*	

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 9 of 10

Complete if Known	
Application Number	11/883,218-Conf. #9960
Filing Date	July 27, 2008
First Named Inventor	Witz Missel
Art Unit	N/A
Examiner Name	Not Yet Assigned
Attorney Docket Number	11987-00042-US

		3: 189-208 (1998).	
	CC3	KAISER, B., "Thrombin and Factor Xa Inhibitors," *Drugs of the Future,* 23: 423-426 (1998).	
	CD3	AL-OBEIDI, F., Ostrem, J., "Factor Xa Inhibitors," *Expert Opin. Therapeutic Patents,* 9: 931-953 (1999).	
	CE3	AL-OBEIDI, F., Ostrem, J., "Factor Xa Inhibitors by Classical and Combinatorial Chemistry," *DDT,* 3: 223-231 (May 1998).	
	CF3	HAUPTMANN, J.,et al., "Synthetic Inhibitors of Thrombin and Factor Xa: From Bench to Bedside," *Thrombosis Research* , 93: 203-241 (1999).	
	CG3	Pschyrembel, Klinisches Worterbuch, 257. Auflage, 1994, Walter de Gruyter Verlag, p. 199-200, Stichwort "Blutgerinnung."	
	CH3	Rompp Lexikon Chemie, Ver. 1.5, 1998, Georg Thieme Verlag Stuttgart, Stichwort "Blutgerrinung" Lubert Stryer, Biochemie, Spektrum der Wissenschaft Verlagsgesellschaft mbH Heidelberg, 1990, p. 259.	
	CI3	Pschyrembel, Klinisches Worterbuch, 257. Auflage, 1994, Walter de Gruyter Verlag, p. 610, Stichwort "Heparin."	
	CJ3	Rompp Lexikon Chemie, Ver. 1.5, 1998, Georg Thieme Verlag Stuttgart, Stichwort "Heparin."	
	CK3	Pschyrembel, Klinisches Worterbuch, 257. Auflage, 1994, Walter de Gruyter Verlag, p. 292, Stichwort "Cumarinderivate."	
	CL3	BECKER, M.R., et al., "Synthesis, Sar and in Vivo Activity of Novel Thienopyridine Sulfonamide Pyrrolidininones as Factor Xa Inhibitors," *Bioorganic and Medicinal Chemistry Letters,* 9: 2753-2758 (1999).	
	CM3	LINDER, J., et al., "Delayed Onset of Inflammation in Protease-Activated Receptor-2-Deficient Mice," J. Immunology, 2000, pp. 6504-6510.	
	CN3	CIRINO, G. et al. "Inflammation-Coagulation Network: Are Serine Protease receptors the knot?; Tips; 200, vol.21, pp. 170-172	
	CO3	ROEHRIG, S. et al. Discovery of the Novel Antithrombotic Agent 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)thiophene-2-carboxamide (BAY 59-7939): An Oral, Direct Factor Xa Inhibitor. J. Med. Chem. 48, 22. Sept. 2005, pp. 5900-5908.	
	CP3	CAIRA, M. Crystalline Polymorphism Of Organic Compounds. Springer Verlag Berlin Heidelberg 198, 1998, pp. 163-208.	
	CQ3	HANCOCK, B. et al. Characteristics and Significance of the Amorphous State in Pharmaceutical Systems. Journal of Pharmaceutical Science. 86, 1 (1997-1), pp. 1-12.	
	CR3	CHIOU, W.L. et al. Pharmaceutical Applications of Solid Dispersion Systems. Journal of Pharmaceutical Sciences 60, (1971). 128-1302.	
	CS3	FORD, J.L. The Current Status of Solid Dispersions. Pharm Acta Helv. 61, (1986)69-88.	
	CT3	RASENACK, N. et al. Poorly Water-soluble Drugs for Oral Delivery- A Challenge for Pharmaceutical Development. Pharmazeutische Industrie 67, Nr. 5 (2005), 583-591.	
	CU3	BREITENBACH, J. Melt extrusion: from process to drug delivery technology. European Journal of Pharmaceutics and Biopharmaceutics 54 (2002) 107-117.	
	CV3	BREITENBACH, J. Feste Loesungen durch Schmelzextrusion - ein integriertes Herstellkonzept. Pharmazie in unserer Zeit 29 (2000), 46-49.	
	CW3	http://familydoctor.org/online/famdocen/home/common/heartdisease/basics/290.html	
	CX3	LERK, et al., Effect of Hydrophilization Drugs on Release Rat from Capsules, J. of Pharma. Sciences, 67(7), pp. 935-939 (1978)	
	CY3	LERK, et al., *In Vitro and In Vivo* Availability of Hydrophilized Phenytoin from Capsules, J. of Pharma. Sciences, 68(5), pp. 634-638 (1979)	
	CZ3	GREAVES, et al., Novel Approaches to the Preparation of Low-Dose Solid Dosage Forms,Pharmaceutical Technology. January, pp. 60-64, (1995)	

PTO/SB/08b (08-08)
Approved for use through 08/31/2008. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 10 of 10

Complete if Known	
Application Number	11/883,218-Conf. #9960
Filing Date	July 27, 2008
First Named Inventor	Witz Missel
Art Unit	N/A
Examiner Name	Not Yet Assigned
Attorney Docket Number	11987-00042-US

	CA4	REPPE, et al., Justus Liebigs Ann. Chem. 596, 1955, p. 209.	
	CB4	WONG et al., The Journal of Pharmacology and Expermental Therapeutics, Vol. 295, No. 1 (2000) pages 212-218.	
	CC4	[Database Bielstein] Bielstein Institute for Organic Chemistry, Frankfurt-Main, DE. Database Accession No. 8822985.	
	CD4	PERZBORN, E. et al. *In vitro* and *in vivo* studies of the novel antithrombotic agent BAY 59-7939-an oral, direct Factor Xa inhibitor. Journal of Thrombosis and Haemostasis 3, 3, March 2005, pp. 514-521.	
	CE4	ESPINOSA, G. et al. Thrombotic microangiopathic haemolytic anaemia and antiphospholipid antibodies. Annals of the Rheumatic Diseases, 63, 6, June 2004, pp. 730-736.	
	CF4	BONOMINI, V. et al. A New Antithrombotic Agent in the Treatment of Acute Renal Failure Due to Hemolytic-Uremic Syndrome and Thrombotic Thrombocytopenic Purpura. Nephron 37, 1984, 2, 144.	
	CG4	SINHA, U. et al. Antithrombotic and hemostatic capacity of factor Xa versus thrombin inhibitors in models of venous and arteriovenous thrombosis. European Journal of Pharmacology 2000, 395, 51-59.	
	CH4	BETZ, A. Recent advances in Factor Xa inhibitors. Expert Opinion Ther. Patents 2001, 11, 1007-1017.	
	CI4	TAN, K.T. et al. Factor X inhibitors. Expert Opinion Investig. Drugs 2003, 12, 799-804.	
	CJ4	RUEF, J. et al. New antithrombotic drugs on the horizon. Expert Opinion Investig. Drugs 2003, 12, 781-797.	
	CK4	SAMAMA, M.L. Synthetic direct and indirect factor Xa inhibitors. Thromobis Research 2002, 106, V267-V273.	
	CL4	QUAN, M.L. The race to an orally active Factor Xa inhibitor: Recent advances. Current Opinion in Drug Discovery & Development 2004, 7, 460-469.	
	CM4	The Ephesus Study, Blood 2000, 96, 490a	
	CN4	The Penthifra Study, Blood 2000, 96, 490a	
	CO4	The Pentamaks Study, Blood 2000, 96, 490a-491a.	
	CP4	The Pentathlon 2000 Study, Blood 2000, 96, 491a	
	CQ4	LEADLEY, R.J. Coagulation Factor Xa Inhibition: Biological Background and Rationale. Current Topics in Medical Chemistry 2001, 1, 151-159.	
	CR4	GILLIGAN, D.M. et al. The Management of Atrial Fibrillation. The American Journal of Medicine, vol. 101, (4) 1996, 413-421.	
	CS4	KUBITZA, D. et al. Novel factor Xa inhibitors for prevention and treatment of thromboembolic diseases. Expert Opinion on Investig. Drugs, vol. 15, (8) 2006, pp. 843-855.	
	CT4	WILLIAMS, E.M. Vaughan. Classificating anti-arrhythimic drugs. In: Cardiac Arrythias-Proceedings of a symposium, sandoe E., soedertaeje: Astra (1970), pp. 449-469.	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1]Applicant's unique citation designation number (optional). [2]Applicant is to place a check mark here if English language Translation is attached.

(51) Int. Cl. 2: C 07 D 263/24
C 07 D 317/22
C 07 D 405/12
A 61 K 31/42

(19) BUNDESREPUBLIK DEUTSCHLAND
DEUTSCHES PATENTAMT

DE 28 36 305 A1

(11) Offenlegungsschrift 28 36 305

(21) Aktenzeichen: P 28 36 305.5
(22) Anmeldetag: 18. 8. 78
(43) Offenlegungstag: 1. 3. 79

(30) Unionspriorität:
(32) (33) (31) 26. 8. 77 Frankreich 7726105 23. 5. 78 Frankreich 7815342

(54) Bezeichnung: 5-Hydroxymethyl-2-oxazolidinone, Verfahren zu ihrer Herstellung und sie enthaltende Arzneimittel

(61) Zusatz zu: P 27 08 236.6

(71) Anmelder: Delalande S.A., Courbevoie, Hautsde-Seine (Frankreich)

(74) Vertreter: Grünecker, A., Dipl.-Ing.; Kinkeldey, H., Dr.-Ing.; Stockmair, W., Dr.-Ing. Ae.E.; Schumann, K., Dipl.-Phys. Dr.rer.nat.; Jakob, P., Dipl.-Ing.; Bezold, G., Dipl.-Chem. Dr.rer.nat.; Pat.-Anwälte, 8000 München

(72) Erfinder: Dostert, Philippe, Chaville; Douzon, Colette, Paris; Bourgery, Guy, Colombes; Gouret, Claude, Meudon; Mocquet, Gisele, Paris; Coston, Jean-Alain, Garches (Frankreich)

DE 28 36 305 A1

© 2. 79 909 809/1016 22/100

PATENTANWÄLTE

A. GRÜNECKER
DIPL.-ING.
H. KINKELDEY
DR.-ING.
W. STOCKMAIR
DR.-ING. · AsE (CALTECH)
K. SCHUMANN
DR. RER. NAT. · DIPL.-PHYS.
P. H. JAKOB
DIPL.-ING.
G. BEZOLD
DR. RER. NAT. · DIPL.-CHEM.

8 MÜNCHEN 22
MAXIMILIANSTRASSE 43

2836305

Zusatz zu P 27 08 236.6

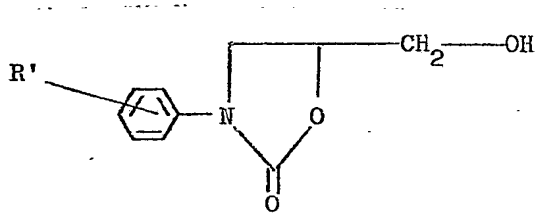
18. Aug. 1978

P 13 032

DELALANDE S.A.
32, rue Henri Regnault, F-92402 COURBEVOIE

Patentansprüche

1. 5-Hydroxymethyl-2-oxazolidinone, gekennzeichnet durch die allgemeine Formel



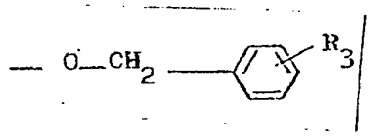
(I')

worin bedeuten:

R' - eine p-Amino-, m-Dimethylamino-, p-n-Pentylamino-, p-Trifluormethyl-, p-Phenoxymethylgruppe, deren Phenylkern gegebenenfalls in der 3-Stellung durch eine Nitrogruppe substituiert ist, eine p-(m-Chlorphenyläthyl)-, p-Styryl(trans)- oder 2-p-Methyl-2-methylthio-1,3-dioxolan-Gruppe;

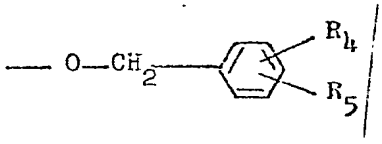
- eine $-SR_1$-Gruppe, die in der p-Stellung angeordnet ist und in der R_1 eine Alkylgruppe mit 5 Kohlenstoffatomen oder eine Acetylmethylthiogruppe darstellt;

- eine $-OR_2$-Gruppe, die in der p-Stellung angeordnet ist und in der R_2 darstellt
  - eine Isopentyl-, Neopentyl-, 3,3-Dimethylbutyl- oder 2-Äthylbutylgruppe,
  - eine Cycloalkylmethylgruppe, in der die Cycloalkylgruppe 3 bis 7 Kohlenstoffatome aufweist, oder eine Cycloalkyläthylgruppe, in der die Cycloalkylgruppe 5 oder 6 Kohlenstoffatome aufweist,
  - eine 4-Pentenylgruppe,
  - eine 1-Cycloalkenmethylgruppe mit 6 oder 7 Kohlenstoffatomen, eine 1-Methylcyclopentylmethyl- oder 1,4-Cyclohexadienylmethylgruppe oder
  - eine 2-1,3-Dioxolanylmethyl-, 2-1,3-Dithiolanylmethyl-, 2-1,3-Oxathiolanylmethyl-, 2-1,3-Dithianylmethyl-, 2-Tetrahydropyranylmethyl-, 3-Tetrahydropyranylmethyl- oder 4-Tetrahydropyranylmethylgruppe;
- eine Benzyloxygruppe, die in der p-Stellung substituiert ist und die Formel hat



worin R_3 einen Rest darstellt, der ausgewählt wird aus der Gruppe o-Cyano, m-Chlor, m-Brom, m-Jod, m-Nitro, m-Cyano, p-Acetamido, m-Amino, $p\text{-}NHCOOCH_3$, $p\text{-}NHCOC_2H_5$;

- eine Benzyloxygruppe, die in der p-Stellung disubstituiert ist und die Formel hat



worin das Paar (R_4, R_5) eine Bedeutung hat, die ausgewählt wird aus der folgenden Gruppe: (3-Cl, 4-Cl), (2-Cl, 4-Cl), (3-Cl, 5-Cl), (3-Cl, 4-F), ($3NO_2$, 4-F), ($3-NO_2$, 5-CN), ($3-NO_2$, 5-Cl), ($3-NO_2$, 4-Cl), (3-Cl, $4-NO_2$), (3-CN, 4-F);

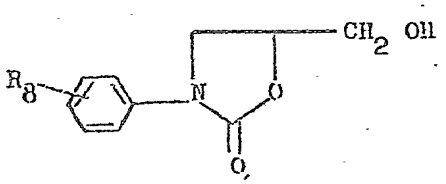
- eine heterocyclische Methyloxykette, die in der p-Stellung angeordnet ist und die Formel hat

$$Het - CH_2O -$$

worin Het eine der folgenden Reste darstellt: 2-Pyridyl, 3-Pyridyl, 4-Pyridyl, 2-Thienyl, 3-Thienyl, 2-Furyl, 3-Furyl, 2-Pyrazinyl;

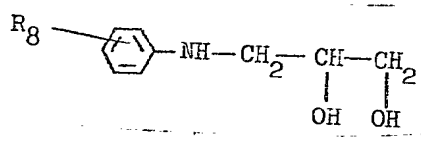
- eine $-COR_6$-Kette, die in der p-Stellung angeordnet ist und in der R_6 eine Alkylgruppe mit 2 bis 3 Kohlenstoffatomen darstellt;
- eine $-O-CH_2-CO-R_7$-Kette, die in der m- oder p-Stellung angeordnet ist und in der R_7 eine Alkylgruppe mit 1 bis 3 Kohlenstoffatomen darstellt;
- eine $-O-(CH_2)_n-CN$-Kette, die in der m- oder p-Stellung angeordnet ist und in der n die Zahl 1, 2, 3 oder 4 bedeutet; oder
- eine in der p-Stellung angeordnete Kette, die ausgewählt wird aus der folgenden Gruppe: Methoxymethyloxy, 2-Morpholinoäthyloxy, Acetylmethyloxyoxim.

2. Verfahren zur Herstellung von 5-Hydroxymethyl-2-oxazolidinonen der allgemeinen Formel



(Ia)

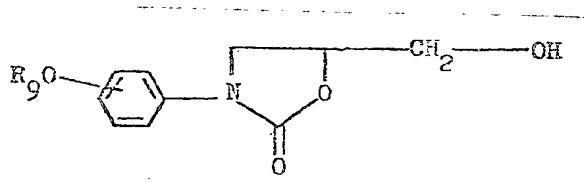
worin R_8 eine m-Dimethylamino-, p-Phenoxymethyl-, p-Trifluormethyl-, p-(m-Chlorphenyläthyl)- oder p-Styryl(trans)-Gruppe; eine in p-Stellung angeordnete $-SR_1$-Gruppe, worin R_1 eine Alkylgruppe mit 5 Kohlenstoffatomen darstellt, oder eine in p-Stellung angeordnete $-COR_6$-Kette, worin R_6 eine Alkylgruppe mit 2 bis 3 Kohlenstoffatomen darstellt, bedeutet, dadurch gekennzeichnet, daß man ein 1-Phenylamino-2,3-propandiol der allgemeinen Formel



(II)

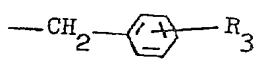
worin R_8 die oben in bezug auf die Formel (Ia) angegebenen Bedeutung hat, durch Einwirkung von Äthylcarbonat cyclisiert.

3. Verfahren zur Herstellung von 5-Hydroxymethyl-2-oxazolidinonen der allgemeinen Formel

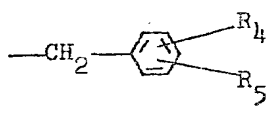


(I_b)

worin R_9 die gleichen Bedeutungen hat wie R_2 in der in Anspruch 1 angegebenen Formel (I') mit Ausnahme der 2-1,3-Dithiolanylmethyl-, 2-1,3-Oxathiolanylmethyl- und 2-1,3-Dithianylmethyl-Gruppen oder eine substituierte Benzylgruppe der Formel



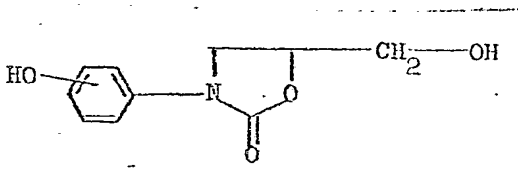
worin R_3 die gleichen Bedeutungen wie in der Formel (I') in Anspruch 1 hat, eine disubstituierte Benzylgruppe der Formel



worin R_4 und R_5 die gleichen Bedeutungen wie in der Formel (I') in Anspruch 1 haben, eine heterocyclische Methylkette der Formel

$$Het - CH_2 -$$

worin Het die gleichen Bedeutungen wie in der Formel (I') in Anspruch 1 hat, eine $-CH_2-CO-R_7-$Kette, worin R_7 die gleichen Bedeutungen wie in der Formel (I') in Anspruch 1 hat, oder eine Gruppe bedeutet, die ausgewählt wird aus den Methoxymethyl-, 2-Morpholinoäthyl-, Cyanomethyl-, 3-Cyanopropyl-, 4-Cyanobutylgruppen, dadurch gekennzeichnet, daß man eine Verbindung der allgemeinen Formel

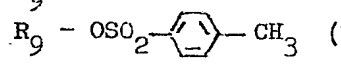


(V)

vorzugsweise unter Rückfluß in Aceton oder Acetonitril und in Gegenwart von Kaliumcarbonat mit einer Verbindung einer der folgenden Formeln kondensiert

$R_9 - Cl$ (VI)

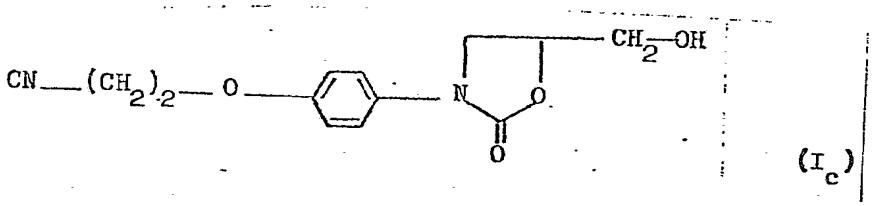
$R_9 - Br$ (VII)



(VIII)

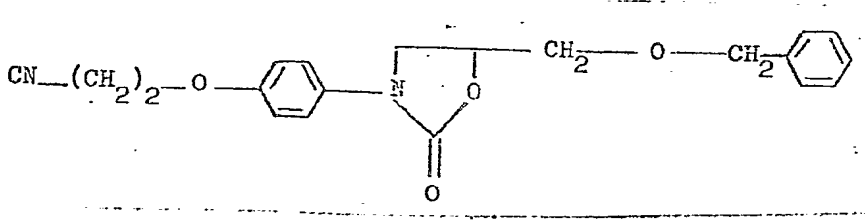
worin R_9 die oben angegebenen Bedeutungen hat.

4. Verfahren zur Herstellung eines 5-Hydroxymethyl-2-oxazolidinons der Formel



(I_c)

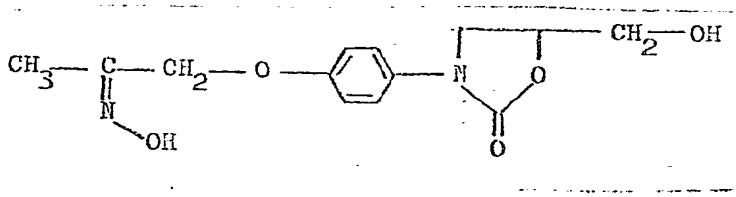
dadurch gekennzeichnet, daß man eine Verbindung der Formel



(XIII)

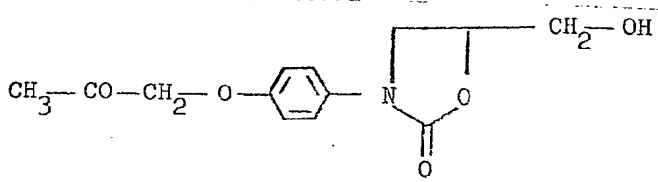
in Äthanol in Gegenwart von Palladium auf Kohle und vorzugsweise in Gegenwart von einigen Tropfen salzsaurem Äthanol der Hydrogenolyse unterwirft.

5. Verfahren zur Herstellung des 5-Hydroxymethyl-2-oxazolidinons der Formel



(I_d)

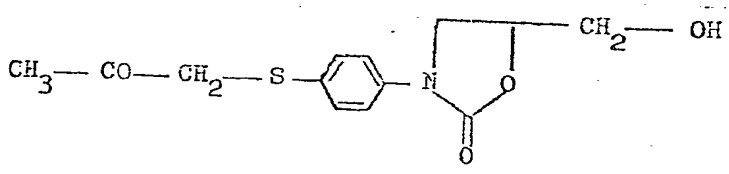
dadurch gekennzeichnet, daß man die nach dem Verfahren des Anspruchs 3 hergestellte Verbindung der Formel



(I'_b)

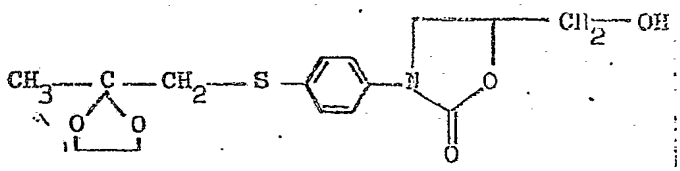
mit Hydroxylaminhydrochlorid in wäßrigem Äthanol kondensiert.

6. Verfahren zur Herstellung des 5-Hydroxymethyl-2-oxazolidinons der Formel



(I_c)

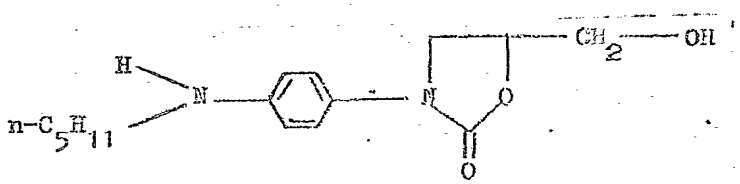
dadurch gekennzeichnet, daß man die Verbindung der Formel



(XV)

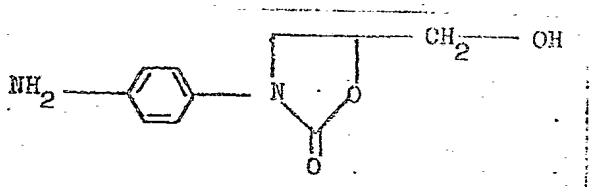
in Gegenwart von konzentrierter Chlorwasserstoffsäure in Tetrahydrofuran hydrolysiert.

7. Verfahren zur Herstellung des 5-Hydroxymethyl-2-oxazolidinons der Formel



(I_f)

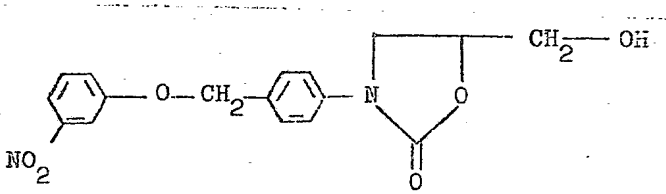
dadurch gekennzeichnet, daß man die Verbindung der Formel



(XVIII)

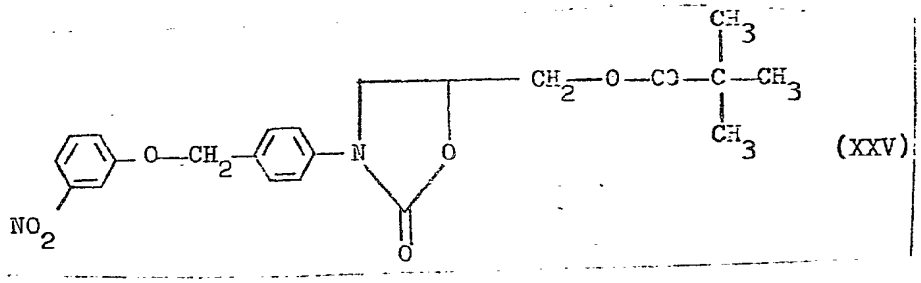
in Butanol und in Gegenwart von Kaliumcarbonat mit n-Pentylbromid kondensiert.

8. Verfahren zur Herstellung des 5-Hydroxymethyl-2-oxazolidinons der Formel



(I_g)

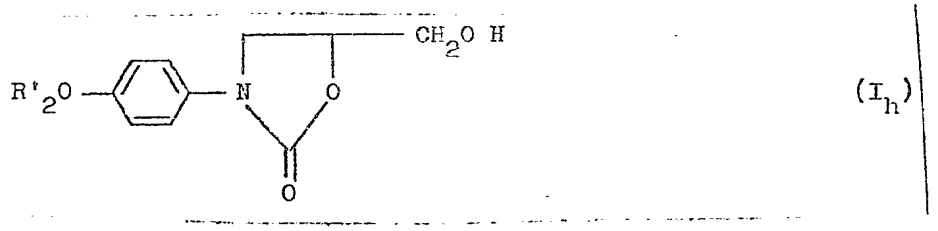
dadurch gekennzeichnet, daß man die Verbindung der Formel



(XXV)

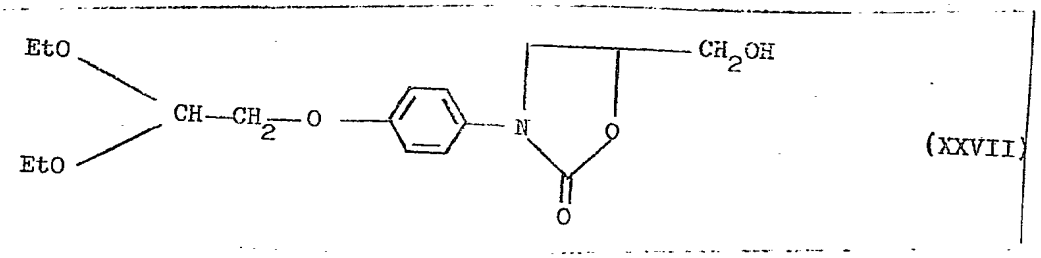
hydrolysiert.

9. Verfahren zur Herstellung der 5-Hydroxymethyl-2-oxazolidinone der allgemeinen Formel



(I_h)

worin R'_2 eine 2-1,3-Dithiolanylmethyl-, 2-1,3-Oxathiolanylmethyl- oder 2-1,3-Dithianylmethyl-Gruppe bedeutet,
dadurch gekennzeichnet, daß man die Verbindung der Formel



(XXVII)

worin Et den Äthylrest bedeutet, mit einer Verbindung der Formel umsetzt

(XXVIII)

worin das Paar (n, X) die folgenden Bedeutungen haben kann: (1, Schwefel), (1, Sauerstoff), (2, Schwefel).

10. Arzneimittel, insbesondere für die Behandlung von endogenen und exogenen depressiven Zuständen, dadurch gekennzeichnet, daß es mindestens eine Verbindung der in Anspruch 1 angegebenen allgemeinen Formel (I') mit Ausnahme der Verbindungen, in denen R' eine p-Amino- oder 2-p-Methyl-2-methylthio-1,3-dioxolan-Gruppe bedeutet, als Wirkstoff, enthält.

PATENTANWÄLTE

A. GRÜNECKER
DR.-ING.
H. KINKELDEY
DR.-ING.
W. STOCKMAIR
DR.-ING. · AsE (CALTECH)
K. SCHUMANN
DR. RER. NAT. · DIPL.-PHYS.
P. H. JAKOB
DIPL.-ING.
G. BEZOLD
DR. RER. NAT. · DIPL.-CHEM.

8 MÜNCHEN 22
MAXIMILIANSTRASSE 43

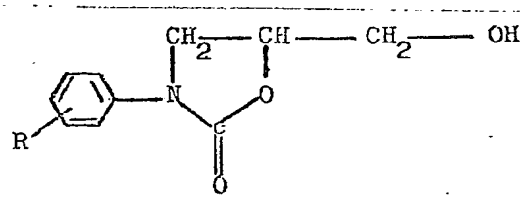
2836305

10

5-Hydroxymethyl-2-oxazolidinone, Verfahren zu ihrer Herstellung und sie enthaltende Arzneimittel

Die Erfindung betrifft neue 5-Hydroxymethyl-2-oxazolidinone, Verfahren zu ihrer Herstellung und ihre therapeutische Verwendung bzw. sie enthaltende pharmazeutische Mittel.

Die einen Gegenstand der Erfindung bildenden neuen Verbindungen sind gekennzeichnet durch die allgemeine Formel



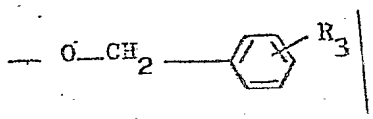
(I)

worin bedeuten:

TELEFON (089) 22 28 62 TELEX 05-29 380 TELEGRAMME MONAPAT TELEKOPIERER

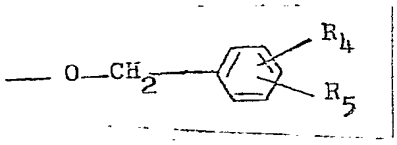
R - eine m-Dimethylamino-, p-n-Pentylamino-, p-Trifluormethyl-, p-Phenoxymethyl-Gruppe, deren Phenylkern in der 3-Stellung gegebenenfalls substituiert ist durch eine Nitrogruppe, eine p-(m-Chlorphenyläthyl)- oder p-Styryl(trans)-Gruppe;

- eine in der p-Stellung angeordnete $-SR_1$-Gruppe, in der R_1 eine Alkylgruppe mit 5 Kohlenstoffatomen oder eine Acetylmethylthiogruppe darstellt;
- eine in der p-Stellung angeordnete $-OR_2$-Gruppe, in der R_2 darstellt:
  - eine Isopentyl-, Neopentyl-, 3,3-Dimethylbutyl- oder 2-Äthylbutylgruppe,
  - eine Cycloalkylmethylgruppe, worin der Cycloalkylrest 3 bis 7 Kohlenstoffatome enthält, oder eine Cycloalkyläthylgruppe, worin der Cycloalkylrest 5 oder 6 Kohlenstoffatome enthält,
  - eine 4-Pentenylgruppe,
  - eine 1-Cycloalkenmethylgruppe mit 6 oder 7 Kohlenstoffatomen, eine 1-Methylcyclopentylmethyl- oder 1,4-Cyclohexadienylmethylgruppe oder
  - eine 2-1,3-Dioxolanylmethyl-, 2-1,3-Dithiolanylmethyl-, 2-1,3-Oxathiolanylmethyl-, 2-1,3-Dithianylmethyl-, 2-Tetrahydropyranylmethyl-, 3-Tetrahydropyranylmethyl- oder 4-Tetrahydropyranylmethylgruppe;
- eine in der p-Stellung angeordnete substituierte Benzyloxygruppe der Formel



worin R_3 einen Rest darstellt, der ausgewählt wird aus der Gruppe: o-Cyano, m-Chlor, m-Brom, m-Jod, m-Nitro, m-Cyano, p-Acetamido, m-Amino, p-$NHCOOCH_3$, p-$NHCOC_2H_5$;

- eine in p-Stellung angeordnete disubstituierte Benzyloxygruppe der Formel



worin das Paar (R_4, R_5) eine Bedeutung hat, die ausgewählt wird aus der Gruppe: (3-Cl, 4-Cl), (2-Cl, 4-Cl), (3-Cl, 5-Cl), (3-Cl, 4-F), (3-NO_2, 4-Cl), (3-Cl, 4-NO_2), (3-CN, 4-F), (3-NO_2, 4-F), (3-NO_2, 5-CN), (3-NO_2, 5-Cl);

- eine in der p-Stellung angeordnete heterocyclische Methyloxykette der Formel

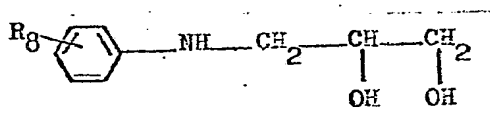
$$Het - CH_2O -$$

worin Het einen der folgenden Reste darstellt: 2-Pyridyl, 3-Pyridyl, 4-Pyridyl, 2-Thienyl, 3-Thienyl, 2-Furyl, 3-Furyl, 2-Pyrazinyl;

- eine in der p-Stellung angeordnete $-COR_6$-Kette, worin R_6 eine Alkylgruppe mit 2 bis 3 Kohlenstoffatomen darstellt;
- eine in der m- oder p-Stellung angeordnete $-O-CH_2-CO-R_7-$ Kette, worin R_7 eine Alkylgruppe mit 1 bis 3 Kohlenstoffatomen darstellt;
- eine in der m- oder p-Stellung angeordnete $-O-(CH_2)_n-CN-$ Kette, worin n die Zahl 1, 2, 3 oder 4 bedeutet; oder
- eine in der p-Stellung angeordnete Kette, die ausgewählt wird aus der Gruppe: Methoxymethyloxy, 2-Morpholinoäthyloxy, Acetylmethyloxyoxim.

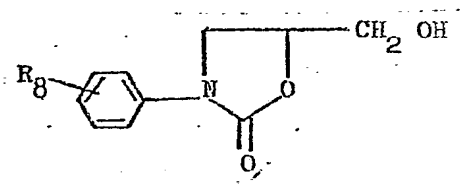
Die Verbindungen der oben angegebenen Formel (I) werden erhalten:

a) Durch Cyclisieren eines 1-Phenylamino-2,3-propandiols der Formel



(II)

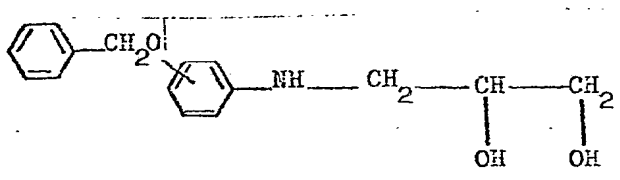
worin R_8 eine m-Dimethylamino-, p-Phenoxymethyl-, p-Trifluormethyl-, p-(m-Chlorphenyläthyl)- oder p-Styryl(trans)-Gruppe, eine in der p-Stellung angeordnete $-SR_1$-Gruppe, worin R_1 eine Alkylgruppe mit 5 Kohlenstoffatomen darstellt, oder eine in der p-Stellung angeordnete $-COR_6$-Kette, worin R_6 eine Alkylgruppe mit 2 bis 3 Kohlenstoffatomen darstellt,
durch Einwirkung von Äthylcarbonat, vorzugsweise in Gegenwart einer Base und eines organischen Lösungsmittels, was zu Verbindungen der Formel führt



(Ia)

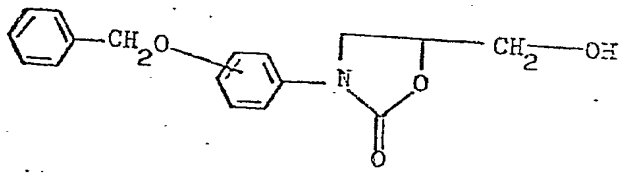
worin R_8 die oben angegebenen Bedeutungen hat:

b) durch Cyclisieren von 1-Phenylamino-2,3-propandiol der Formel



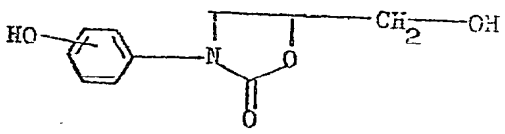
(III)

durch Einwirkung von Äthylcarbonat, was zu der Verbindung der Formel führt



(IV)

die anschließend in Gegenwart von Palladium auf Kohle in Alkohol einer Hydrogenolyse unterworfen wird unter Bildung der Verbindung der Formel

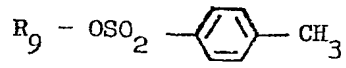


(V)

die man, vorzugsweise unter Rückfluß in Aceton oder Acetonitril und in Gegenwart von Kaliumcarbonat, mit einer Verbindung einer der folgenden Formeln kondensiert

$R_9 - Cl$ (VI)

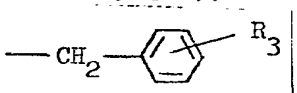
$R_9 - Br$ (VII)



(VIII)

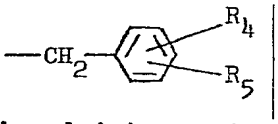
worin R_9 die gleichen Bedeutungen wie R_2 in der Formel (I) hat mit Ausnahme der 2-1,3-Dithiolanylmethyl-, 2-1,3-Oxathiolanylmethyl- und 2-1,3-Dithianylmethyl-Gruppen oder worin R_9 bedeutet:

- eine substituierte Benzylgruppe der Formel



worin R_3 die in der Formel (I) angegebenen Bedeutungen hat,

- eine disubstituierte Benzylgruppe der Formel



worin R_4 und R_5 die gleichen Bedeutungen wie in der Formel (I) haben,

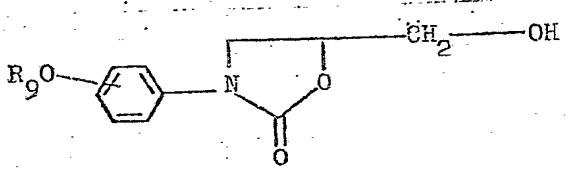
- eine heterocyclische Methylkette der Formel

$$Het - CH_2 -$$

worin Het die gleichen Bedeutungen wie in der Formel (I) hat,

- eine $-CH_2-CO-R_7-$Kette, worin R_7 die gleichen Bedeutungen wie in der Formel (I) hat, oder
- eine Gruppe, die ausgewählt wird aus Methoxymethyl, 2-Morpholinoäthyl, Cyanomethyl, 3-Cyanopropyl, 4-Cyanobutyl,

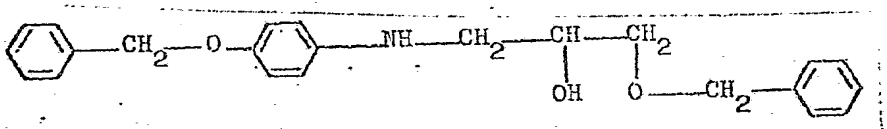
was zu Verbindungen der Formel führt



(Ib)

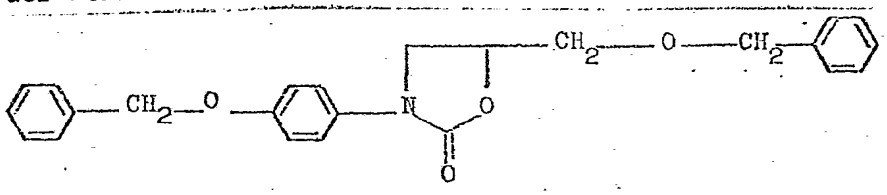
worin R_9 die gleichen Bedeutungen wie oben hat;

c) durch Cyclisieren von 1-Phenylamino-2,3-propandiol der Formel



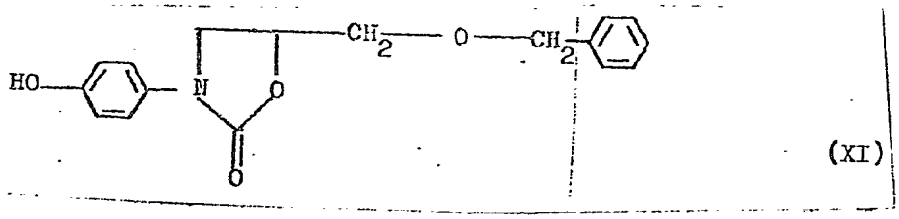
(IX)

durch Einwirkung von Äthylcarbonat, was zu einer neuen Verbindung der Formel führt



(X)

die in Äthanol in Gegenwart von Palladium auf Kohle, vorzugsweise bei Umgebungstemperatur, einerselektiven Hydrogenolyse unterworfen wird unter Bildung der neuen Verbindung der Formel

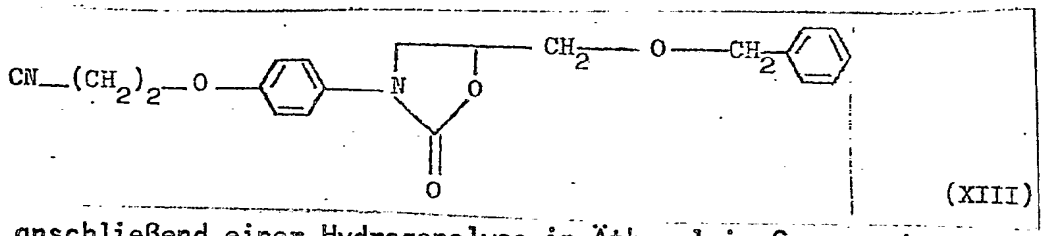


(XI)

die man mit Acrylnitril der Formel

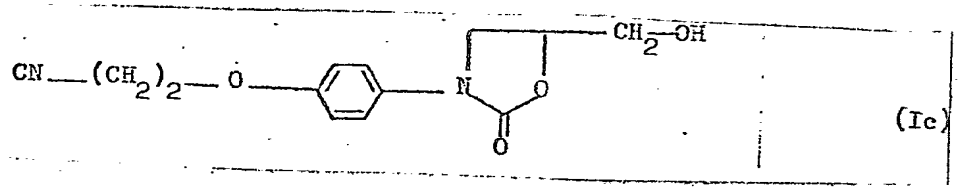
$$CH_2=CH-CN \qquad (XII)$$

in Gegenwart von Triton B kondensiert, was zu der neuen Verbindung der Formel führt



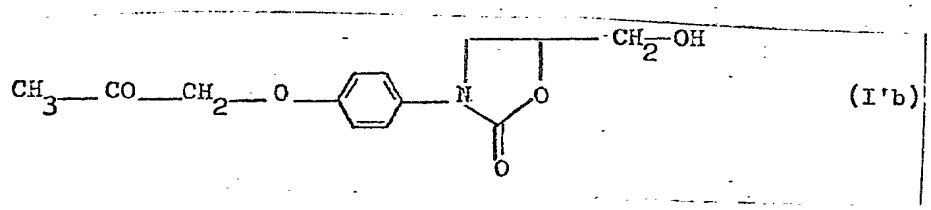
(XIII)

die anschließend einer Hydrogenolyse in Äthanol in Gegenwart von Palladium auf Kohle und vorzugsweise in Gegenwart von einigen Tropfen salzsaurem Äthanol unterworfen wird unter Bildung der Verbindung der Formel



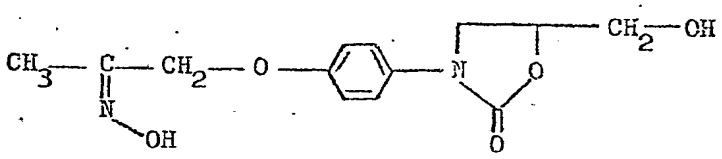
(Ic)

d) durch Kondensieren der Verbindung der Formel



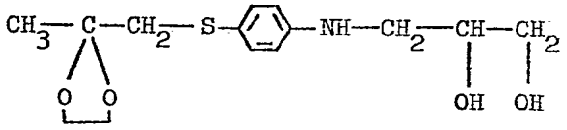
(I'b)

die in dem obigen Abschnitt (b) erhalten worden ist, mit Hydroxylaminhydrochlorid in wäßrigem Äthanol, was zu der Verbindung der Formel führt



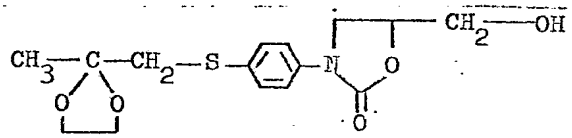
(Id)

e) durch Cyclisieren der Verbindung der Formel



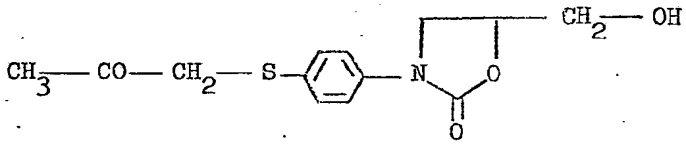
(XIV)

durch Einwirkung von Äthylcarbonat, was zu der neuen Verbindung der Formel führt



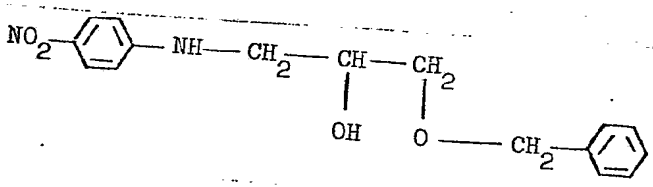
(XV)

die anschließend in Gegenwart von konzentrierter Chlorwasserstoffsäure in Tetrahydrofuran hydrolysiert wird unter Bildung der Verbindung der Formel



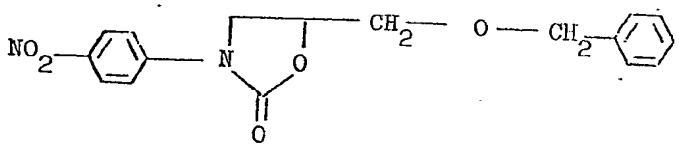
(Ie)

f) durch Cyclisieren der Verbindung der Formel



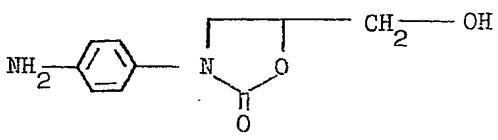
(XVI)

durch Einwirkung von Äthylcarbonat, was zu der neuen Verbindung der Formel führt



(XVII)

die anschließend in Äthanol in Gegenwart von Palladium auf Kohle und vorzugsweise von Äthanol/6,5 n Chlorwasserstoffsäure einer Reduktion und einer gleichzeitigen Hydrogenolyse unterworfen wird unter Bildung der neuen Verbindung der Formel

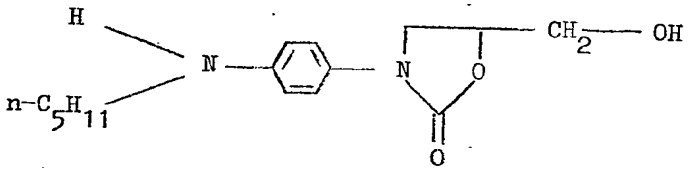


(XVIII)

die man mit n-Pentylbromid der Formel

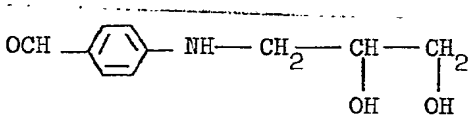
$$C_5H_{11}n - Br \qquad (XIX)$$

in Butanol in Gegenwart von Kaliumcarbonat kondensiert, was zu der Verbindung der Formel führt



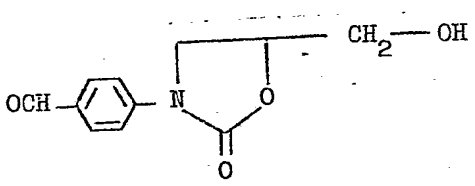
(If)

g) durch Cyclisieren der Verbindung der Formel



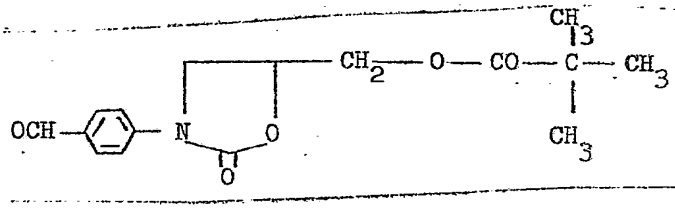
(XX).

in Gegenwart von Äthylcarbonat, insbesondere in Dioxan, indem man die dabei erhaltene Verbindung der Formel



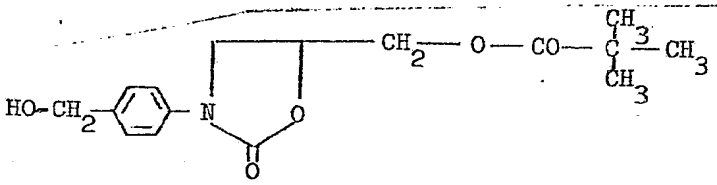
(XXI)

der Einwirkung von tert.-Buttersäurechlorid unterwirft, insbesondere in Pyridin, indem man die dabei erhaltene Verbindung der Formel



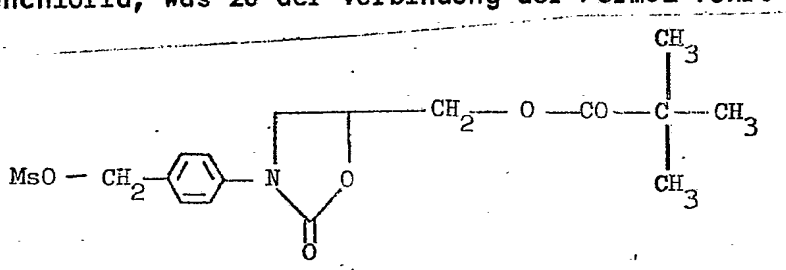
(XXII)

mit Natriumborhydrid, insbesondere in Methanol, reduziert und die dabei erhaltene Verbindung der Formel



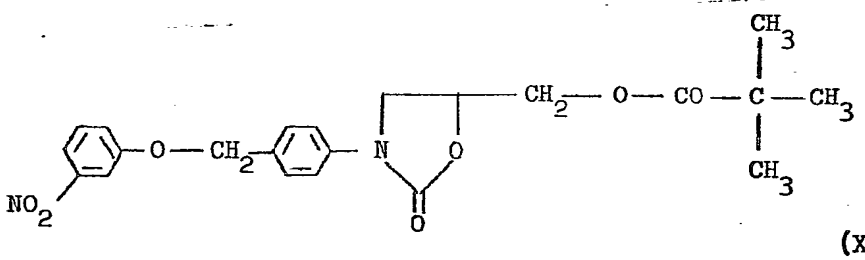
(XXIII)

der Einwirkung von Mesylchlorid unterwirft, insbesondere in Methylenchlorid, was zu der Verbindung der Formel führt



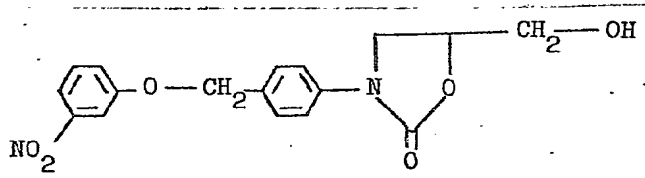
(XXIV)

worin Ms den Mesylrest bedeutet, die man in Gegenwart von Natriumhydrid mit m-Nitrophenol reagieren läßt, die dabei erhaltene Verbindung der Formel



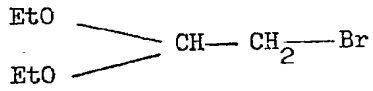
(XXV)

hydrolysiert, vorzugsweise in Gegenwart einer Base, wie Kaliumhydroxid, insbesondere in Methanol, was zu der Verbindung der Formel führt.



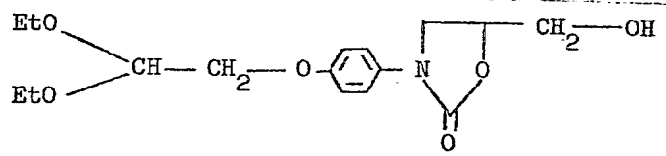
(Ig)

h) durch Kondensieren von Bromacetaldehyddiäthylacetal der Formel



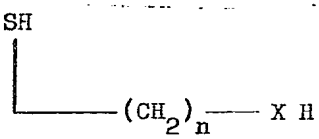
(XXVI)

mit dem in dem obigen Abschnitt (b) erhaltenen 3-p-Hydroxyphenyl-5-hydroxymethyl-2-oxazolidinon der Formel (V') in Gegenwart von Natriumhydrid und eines organischen Lösungsmittels, wie z.B. Dimethylformamid (DMF), die dabei erhaltene Verbindung



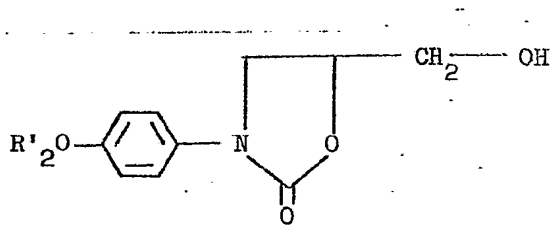
(XXVII)

mit einer Verbindung der Formel umsetzt



(XXVIII)

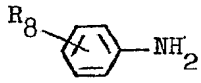
in der das Paar (n, X) die folgenden Bedeutungen annehmen kann: (1, Schwefel), (1, Sauerstoff), (2, Schwefel), vorzugsweise in Gegenwart von Bortrifluoridätherat in Methylenchlorid, was zu Verbindungen der Formel führt



(Ih)

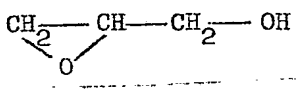
worin R'_2 eine 2-1,3-Dithiolanylmethyl-, 2-1,3-Oxathiolanylmethyl- oder 2-1,3-Dithianylmethylgruppe bedeutet.

Die Verbindungen der Formel II werden ihrerseits erhalten durch Kondensieren von Anilinen der Formel



(XXIX)

worin R_8 die gleichen Bedeutungen wie in der Formel II hat, mit Glycidyl der Formel



(XXX)

in Methanol oder Äthanol.

Die Verbindungen der Formeln (III), (IX), (XIV) und (XVI) werden nach dem gleichen Verfahren hergestellt, wobei jedoch entsprechende Aniline eingesetzt werden.

Es sei noch darauf hingewiesen, daß die Verbindungen der Formeln (I),

(XV) und (XVIII) in den vorstehenden Ansprüchen unter der Formel (I') zusammengefaßt sind.

Die Erfindung wird durch die nachfolgenden Beispiele näher erläutert, ohne jedoch darauf beschränkt zu sein.

Beispiel 1

5-Hydroxymethyl-3-p-trifluormethylphenyl-2-oxazolidinon (I) (Code-Nr. 770 152)

Eine Mischung aus 46 g (0,195 Mol) 3-p-Trifluormethylphenylamino-1,2-propandiol (II), 23,6 g (0,2 Mol) Äthylcarbonat und einigen Tropfen einer 5 %igen methanolischen Natriummethylatlösung in 400 ml Toluol wird 1 Stunde lang auf 105°C erwärmt. Dann verdampft man die Lösungsmittel und chromatographiert den Rückstand an einer Siliciumdioxid-Kolonne (Eluierungsmittel $CHCl_3$), woran sich eine Umkristallisation aus Isopropyläther anschließt; Ausbeute 20 %, Schmelzpunkt (F.) 88°C, Summenformel $C_{11}H_{10}F_3NO_3$, Molekulargewicht 261,19.

Elementaranalyse:

	C	H	N
ber. (%)	50,58	3,86	5,36
gef. (%)	50,74	3,83	5,32

Auf die gleiche Weise kann man die Verbindungen mit den nachfolgend angegebenen Code-Nummern, die in der weiter unten folgenden Tabelle I zusammengefaßt sind, herstellen:
770 365 - 770 423 - 770 696 - 770 180 - 770 155 - 771 181 - 780 564.

Beispiel 2

5-Hydroxymethyl-3-m-cyanomethyloxyphenyl-2-oxazolidinon (Code-Nr. 770 231)

1. Stufe: 5-Hydroxymethyl-3-m-hydroxyphenyl-2-oxazolidinon (V)

In einem Autoklaven unterwirft man eine Lösung von 132,5 g (0,44 Mol) 5-Hydroxymethyl-3-m-benzyloxyphenyl-2-oxazolidinon, hergestellt nach einem Verfahren analog zu demjenigen des Beispiels 1, in 1,5 l Alkohol in Gegenwart von 13 g Palladium auf 10 % Kohle einer Hydrogenolyse zwischen 45 und 50°C. unter einem Druck von 2 kg innerhalb eines Zeitraums von 6 Stunden. Man filtriert, dampft das Filtrat ein und kristallisiert aus Isopropylalkohol um.

2. Stufe: 5-Hydroxymethyl-3-m-cyanomethyloxyphenyl-2-oxazolidinon (Code-Nr. 770 231)

Eine Mischung von 15 g (0,07 Mol) 5-Hydroxymethyl-3-m-hydroxyphenyl-2-oxazolidinon, das in der vorausgegangenen Stufe hergestellt worden ist, 7,6 g (0,1 Mol) Chloracetonitril, 38 g (0,28 Mol) Kaliumcarbonat und 1 g Kaliumjodid in 450 ml Aceton erhitzt man 8 Stunden lang unter Rückfluß. Man filtriert, dampft das Filtrat ein und kristallisiert den Rückstand in absolutem Alkohol; Ausbeute 71 %, F. 110°C, Summenformel $C_{12}H_{12}N_2O_4$, Molekulargewicht 248,23

Elementaranalyse:

	C	H	N
ber. (%)	58,06	4,87	11,29
gef. (%)	58,08	4,90	11,35

Auf die gleiche Weise kann man die Verbindungen mit den nachfolgend angegebenen Code-Nummern, die in der weiter unten folgenden Tabelle zusammengefaßt sind, herstellen:

770 388 - 770 788 - 770 467 - 770 466 -
770 196 - 770 154 - 760 904 - 750 601 - 760 557 - 770 234 -
770 318 - 770 222 - 770 569 - 770 268 - 770 354 - 770 416 -
770 572 - 770 672 - 770 790 - 770 789 - 770 298 - 770 221 -
770 299 - 770 673 - 770 845 - 770 230 - 770 889 - 771 082 -
771 249 - 771 246 - 771 197 - 780 030 - 771 245 - 770 949 -
780 076 - 770 984 - 770 962 - 780 034 - 770 900 - 771 301 -
771 321 - 771 240 - 780 182 - 780 443 - 770 955 - 771 125 -
771 199 - 770 979 - 771 067 - 780 259 - 780 562.

Beispiel 3

3-(2-p-Cyano-äthoxyphenyl)-5-hydroxymethyl-2-oxazolidinon (Code-Nr. 770 131)

1. Stufe: 3-(p-Benzyloxyphenyl)-5-benzyloxymethyl-2-oxazolidinon (Code-Nr. 760 431)

Diese Verbindung wird hergestellt unter Anwendung eines Verfahrens, das identisch mit demjenigen des Beispiels 1 ist, wobei man von dem geeigneten Propandiol ausgeht; Ausbeute 80 %, F. 126°C, Summenformel $C_{24}H_{23}NO_4$, Molekulargewicht 389,43.
Elementaranalyse:

	C	H	N
ber. (%)	74,02	5,95	3,60
gef. (%)	73,87	6,14	3,89

2. Stufe: 3-(p-Hydroxyphenyl)-5-benzyloxymethyl-2-oxazolidinon (Code-Nr. 760 484)

In einem Autoklaven unterwirft man eine Suspension von 18 g (0,046 Mol) der in der vorausgegangenen Stufe hergestellten Verbindung und 2 g Palladium auf 10 % Kohle in 400 ml absolutem Alkohol einer Hydrogenolyse bei Umgebungstemperatur unter einem Druck von 4 bis 5 kg Wasserstoff. Dann filtriert man, dampft das Lösungsmittel ein und kristallisiert aus absolutem Alkohol um; Ausbeute 73 %, F. 153°C, Summenformel $C_{17}H_{17}NO_4$

Elementaranalyse:

	C	H	N
ber. (%)	68,21	5,73	4,68
gef. (%)	68,38	5,62	4,46

3. Stufe: 3-(2-p-Cyanoäthoxyphenyl)-5-benzyloxymethyl-2-oxazolidinon (Code-Nr. 760 993)

Eine Lösung von 13 g (0,03 Mol) der in der vorausgegangenen Stufe hergestellten Verbindung in 45 g (0,86 Mol) Acrylnitril erhitzt man in Gegenwart von 1 ml Triton B (40 %ig in Methanol) 15 Stunden lang unter Rückfluß. Dann dampft man das überschüssige Acrylnitril ein, nimmt den Rückstand in 100 ml 1 n Natriumhydroxid auf, filtriert, wäscht den Niederschlag mit Wasser und dann mit Äther und kristallisiert aus Methanol um; Ausbeute 60 %, F. 112°C, Summenformel $C_{20}H_{20}N_2O_4$

Elementaranalyse:

	C	H	N
ber. (%)	68,17	5,72	7,95
gef. (%)	67,89	5,66	8,21

4. Stufe: 3-(2-p-Cyano-äthoxyphenyl)-5-hydroxymethyl-2-oxazolidinon (Code-Nr. 770 131)

In einem Autoklaven unterwirft man eine Suspension von 3,5 g (0,01 Mol) 3-(2-p-Cyano-äthoxyphenyl)-5-benzyloxymethyl-2-oxazolidinon, das in der vorhergegangenen Stufe hergestellt worden ist, 0,4 g Palladium auf 10 % Kohle und 0,05 ml Äthanol/7,5 n Chlorwasserstoffsäure in 250 ml Dioxan einer Hydrogenolyse unter einem Druck von 1 kg Wasserstoff bei Umgebungstemperatur. Man filtriert, reinigt den Rückstand durch Chromatographie an einer Siliciumdioxidkolonne. Man eluiert mit einem Chloroform/Aceton (50/50)-Gemisch und kristallisiert dann aus absolutem Alkohol um, wobei man 1 g des erwarteten Produkts erhält; Ausbeute 39 %, F. 131°C, Summenformel $C_{13}H_{14}N_2O_4$

Elementaranalyse:

	C	H	N
ber. (%)	59,53	5,38	10,68
gef. (%)	59,06	5,24	10,37

Beispiel 4

3-(p-Acetylmethyloxyphenyl)-5-hydroxymethyl-2-oxazolidinon-oxim (Code-Nr. 770 126)

Eine Lösung von 7 g (0,026 Mol) 3-(p-Acetylmethyloxy)-5-hydroxymethyl-2-oxazolidinon (Code-Nr. 760 652), hergestellt gemäß Beispiel 2, und 2,1 g (0,03 Mol) Hydroxylaminhydrochlorid hält man in einer Mischung aus 120 ml Äthanol und 6 ml Wasser 2 Stunden lang bei Umgebungstemperatur. Dann dampft man das Lösungsmittel ein, nimmt den Rückstand in Wasser auf, filtriert und

kristallisiert aus 96 %igem Alkohol um; Ausbeute 75 %, F. 164°C, Summenformel $C_{13}H_{16}N_2O_5$

Elementaranalyse:

	C	H	N
ber. (%)	55,71	5,75	10,00
gef. (%)	55,44	5,70	10,09

Beispiel 5

3-(p-Acetylmethylthiophenyl)-5-hydroxymethyl-2-oxazolidinon (Code-Nr. 770 501)

1. Stufe: 2-Methyl-p-[3-(5-hydroxymethyl-oxazolidinon)]-2-phenylmercapto-1,3-dioxolan (Code-Nr. 770 500)

Diese Verbindung wird hergestellt unter Anwendung der gleichen Arbeitsweise wie in Beispiel 1, wobei man von dem geeigneten Propandiol ausgeht; F. 140°C, Summenformel $C_{15}H_{19}NO_5S$

Elementaranalyse:

	C	H	N
ber. (%)	55,37	5,89	4,31
gef. (%)	55,36	5,79	4,09

2. Stufe: 3-(p-Acetylmethylthiophenyl)-5-hydroxymethyl-2-oxazolidinon (Code-Nr. 770 501)

Eine Lösung von 10,5 g (0,032 Mol) der in der vorausgegangenen Stufe hergestellten Verbindung in 200 ml Tetrahydrofuran und 10 ml konzentrierter Chlorwasserstoffsäure erhitzt man 30 Minuten lang unter Rückfluß. Dann dampft man das Lösungsmittel ein,