☐ **IDS filed Under 37 CFR 1.97(d)**

In accordance with § 1.97(d), this Information Disclosure Statement is being filed after the mailing date of either a Final Action under § 1.113 or a Notice of Allowance under § 1.311 but before, or simultaneously with, the payment of the Issue Fee, therefore included are: Certification in Accordance with § 1.97(e); and the submission fee of **$180.00** as set forth in § 1.17(p).

CONTENT OF IDS PURSUANT TO 37 CFR 1.98

☒ Copies of reference numbers 1-14 listed on the attached Form PTO-1449 are not required to be submitted pursuant to 37 CFR § 1.98(a)(2)(iii).

☒ Copies of reference numbers 15-25 listed on the attached Form PTO-1449 are enclosed herewith.

☐ Copies of reference numbers are not being submitted because they were previously cited by or submitted to the U.S. Patent and Trademark Office in patent application number , filed for which a claim for priority under 35 U.S.C. § 120 has been made in the instant application.

☐ The month of publication for reference numbers is not available. However, the year of publication for these references is sufficiently earlier than the effective US filing date and any foreign priority date so that the particular month of publication is not in issue pursuant to 37 CFR § 1.98(b).

REFERENCES IN A LANGUAGE OTHER THAN ENGLISH

☐ The following documents are not in the English language. Accordingly, a concise explanation of the relevance of the document was incorporated in the specification passages identified below, the document was identified in a foreign communication as identified below or an English language counterpart application has been provided as indicated below.

Foreign Language Document	Cite No.	Pages of Reference in Specification or Relevance of Document

Foreign Language Document	Cite No.	English Language Counterpart	Cite No.

☐ **CERTIFICATION IN ACCORDANCE WITH § 1.97(e)**

I hereby certify that:

☐ Each item of information contained in this 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 this information disclosure statement.

☐ No item of information contained in this 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 this information disclosure statement was known to any individual designated in § 1.56(c) more than three months prior to the filing of this information disclosure statement.

Please charge any deficiency or credit any overpayment to Deposit Account No. 23-3050.

Date: December 1, 2011

/S. Maurice Valla/
S. Maurice Valla
Registration No. 43,966

WOODCOCK WASHBURN LLP
Cira Centre
2929 Arch Street, 12th Floor
Philadelphia, PA 19104-2891
Telephone: (215) 568-3100
Facsimile: (215) 568-3439

Patent Assignment Abstract of Title

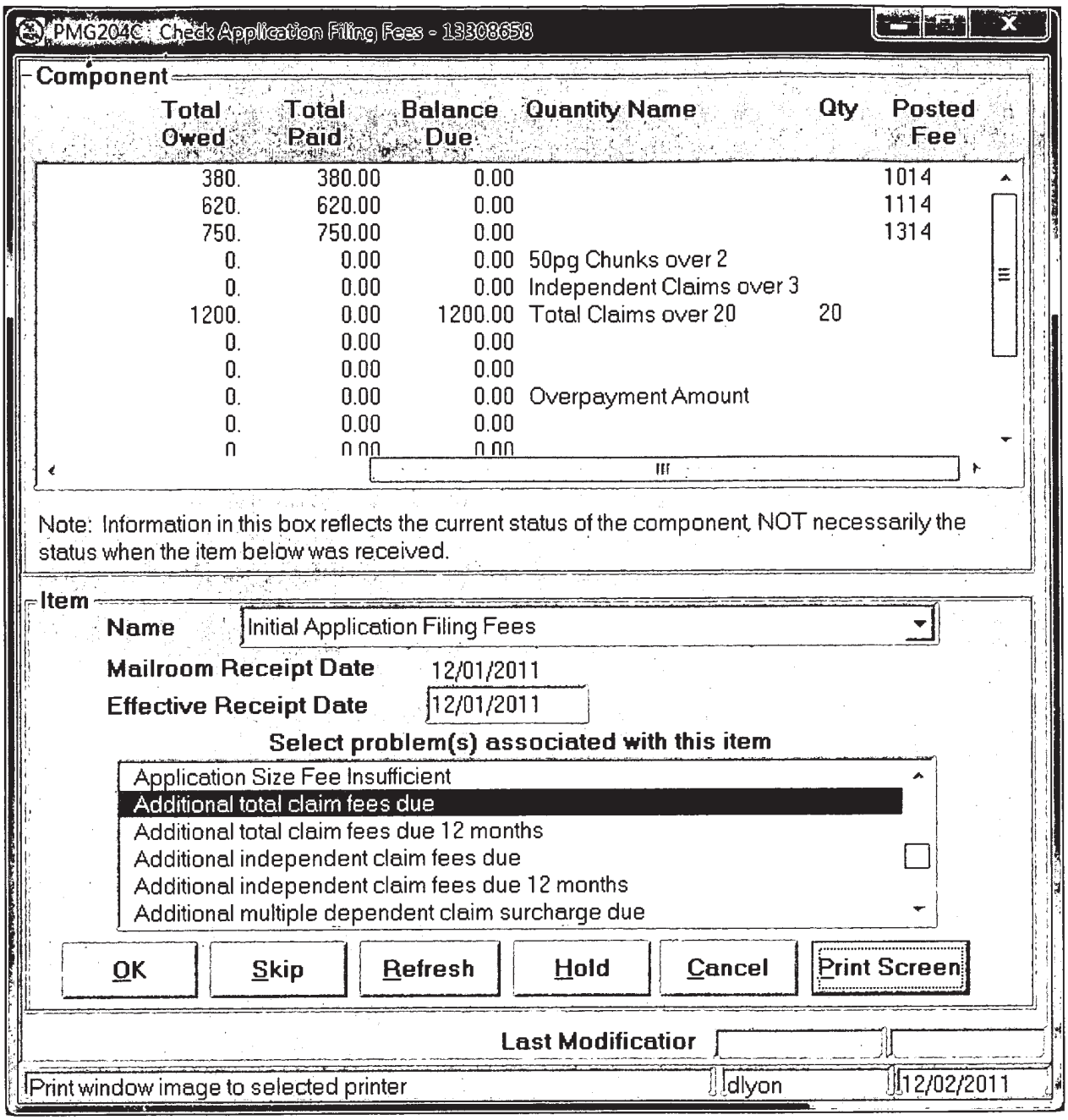
Total Assignments: 1

Application #: 09788173 **Filing Dt:** 02/16/2001 **Patent #:** 6395767 **Issue Dt:** 05/28/2002
PCT #: NONE **Publication #:** US20020019411 **Pub Dt:** 02/14/2002
Inventors: Jeffrey A. Robl, Richard B. Sulsky, David J. Augeri, David R. Magnin, Lawrence G. Hamann, David A. Betebenner
Title: Cyclopropyl-fused pyrrolidine-based inhibitors of dipeptidyl peptidase IV and method

Assignment: 1

Reel/Frame: 011607 / 0369 **Received:** 05/25/2001 **Recorded:** 02/16/2001 **Mailed:** 05/30/2001 **Pages:** 5
Conveyance: ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).
Assignors: ROBL, JEFFREY A. **Exec Dt:** 02/13/2001
SULSKY, RICHARD B. **Exec Dt:** 02/13/2001
AUGERI, DAVID J. **Exec Dt:** 01/14/2001
MAGNIN, DAVID R. **Exec Dt:** 02/13/2001
HAMANN, LAWRRENCE G. **Exec Dt:** 02/13/2001
BETEBENNER, DAVID A. **Exec Dt:** 02/13/2001
Assignee: BRISTOL-MAYERS SQUIBB COMPANY
LAWRENCEVILLE-PRINCETON ROAD
PRINCETON, NEW JERSEY 08543
Correspondent: BRISTOL-MYERS SQUIBB COMPANY
MARLA J. MATHIAS
PATENT DEPARTMENT
P.O. BOX 4000
PRINCETON, NJ 08543-4000

Search Results as of: 12/02/2011 11:44 AM


PMG204C Check Application Filing Fees - 13308658
Component
Total Owed
Total Paid
Balance Due
Quantity Name
Qty
Posted Fee
380. 380.00 0.00 1014
620. 620.00 0.00 1114
750. 750.00 0.00 1314
0. 0.00 0.00 50pg Chunks over 2
0. 0.00 0.00 Independent Claims over 3
1200. 0.00 1200.00 Total Claims over 20 20
0. 0.00 0.00
0. 0.00 0.00
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Note: Information in this box reflects the current status of the component, NOT necessarily the status when the item below was received.
Item
Name
Initial Application Filing Fees
Mailroom Receipt Date
12/01/2011
Effective Receipt Date
12/01/2011
Select problem(s) associated with this item
Application Size Fee Insufficient
Additional total claim fees due
Additional total claim fees due 12 months
Additional independent claim fees due
Additional independent claim fees due 12 months
Additional multiple dependent claim surcharge due
OK
Skip
Refresh
Hold
Cancel
Print Screen
Last Modificatior
Print window image to selected printer
dlyon
12/02/2011

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	Cyclopropyl-Fused Pyrrolidine-Based Inhibitors Of Dipeptidyl Peptidase IV And Method
First Named Inventor/Applicant Name:	Jeffrey A. Robl
Filer:	SAMUEL VALLA/D. McCarty
Attorney Docket Number:	BMS-2856

Filed as Large Entity

Reissue (Utility) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility Reissue Basic	1014	1	380	380
Design and utility Reissue Basic	1114	1	620	620
Design and utility Reissue Basic	1314	1	750	750
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				

12/06/2011 SDIRETA1 00000047 233050 13308658
01 FC:1205 1200.00 DA

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	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
13/308,658	12/01/2011	1629	2950	BMS-2856	40	3

CONFIRMATION NO. 7781

23377
WOODCOCK WASHBURN LLP
CIRA CENTRE, 12TH FLOOR
2929 ARCH STREET
PHILADELPHIA, PA 19104-2891

FILING RECEIPT

OC00000051337996

Date Mailed: 12/19/2011

Receipt is acknowledged of this reissue patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Applicant(s)

Jeffrey A. Robl, Residence Not Provided;

Assignment For Published Patent Application

Bristol-Myers Squibb Company, Princeton, NJ

Power of Attorney: The patent practitioners associated with Customer Number 23377

Domestic Priority data as claimed by applicant

This application is a REI of 09/788,173 02/16/2001 PAT 6395767
which claims benefit of 60/188,555 03/10/2000

Foreign Applications (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.)

If Required, Foreign Filing License Granted: 12/06/2011

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/308,658**

Projected Publication Date: None, application is not eligible for pre-grant publication

Non-Publication Request: No

Early Publication Request: No

Title

Cyclopropyl-Fused Pyrrolidine-Based Inhibitors Of Dipeptidyl Peptidase IV And Method

Preliminary Class

514

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as

set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

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
13/308,658	12/01/2011	Jeffrey A. Robl	BMS-2856

CONFIRMATION NO. 7781

23377
WOODCOCK WASHBURN LLP
CIRA CENTRE, 12TH FLOOR
2929 ARCH STREET
PHILADELPHIA, PA 19104-2891

NOTICE

OC000000051337997

Date Mailed: 12/19/2011

NOTICE OF INFORMAL APPLICATION

This application is considered to be informal since it does not comply with the regulations for the reason(s) indicated below. The period within to correct the informalities noted below and avoid abandonment is set in the accompanying Office action.

Items Required To Avoid Processing Delays:

The item(s) indicated below are also required and should be submitted with any reply to this notice to avoid further processing delays.

A new oath or declaration, identifying this application number, or, if appropriate, an application data sheet (37 CFR 1.76), is required. The oath or declaration does not comply with 37 CFR 1.63 in that it:

- does not identify the residence (e.g., city and either state or foreign country) of each inventor.

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UNITED STATES DEPARTMENT OF COMMERCE
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www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/308,658	12/01/2011	Jeffrey A. Robl	BMS-2856

CONFIRMATION NO. 7781

POA ACCEPTANCE LETTER

23377
WOODCOCK WASHBURN LLP
CIRA CENTRE, 12TH FLOOR
2929 ARCH STREET
PHILADELPHIA, PA 19104-2891

OC000000051287127

Date Mailed: 12/19/2011

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 12/01/2011.

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.

/dalyon/

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
13/308,658	12/01/2011	Jeffrey A. Robl	BMS-2856

CONFIRMATION NO. 7781

POWER OF ATTORNEY NOTICE

46339
BMS/WOODCOCK WASHBURN
PATENT DEPARTMENT
PO BOX 4000
PRINCETON, NJ 08543-4000

OC00000051287074

Date Mailed: 12/19/2011

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 12/01/2011.

- 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).

/dalyon/

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:
Jeffrey A. Robl et al.
Confirmation No.: 7781
Application No.: 13/308,658
Group Art Unit: 1629
Filing Date: December 1, 2011
Examiner:
For: Cyclopropyl-Fused Pyrrolidine-Based Inhibitors Of Dipeptidyl Peptidase IV and Method

Office of Initial Patent Examination
Customer Service Center
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR CORRECTED FILING RECEIPT

1. Attached is a copy of the official filing receipt issued by the U.S. Patent and Trademark Office in connection with the above-referenced re-issue application for which issuance of a corrected filing receipt is respectfully requested. The requested changes are noted thereon, as well as listed below.

2. There is an error with respect to the names and residences of the Applicants.

   (a) Please add the residence for applicant Jeffrey A. Robl which is Newtown, PA (US).

   (b) In addition to Jeffrey A. Robl, there are five additional names that should be listed as applicants and are listed in U.S. Patent No. 6,395,767 which is the subject of this re-issue application. Please add the names listed below:

   Richard B. Sulsky, West Trenton, NJ (US)
   David J. Augeri, Princeton, NJ (US)
   David R. Magnin, Hamilton, NJ (US)
   Lawrence G. Hamann, Cherry Hill, NJ (US)
   David A. Betebenner, Lawrenceville, NJ (US)

Please charge any deficiency or credit any overpayment to Deposit Account No. 23-3050.

Date: January 3, 2012

/S. Maurice Valla/
S. Maurice Valla
Registration No. 43,966

Woodcock Washburn LLP
Cira Centre, 12th Floor
2929 Arch Street
Philadelphia, PA 19104-2891
Telephone: (215) 568-3100
Facsimile: (215) 568-3439

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	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
13/308,658	12/01/2011	1629	2950	BMS-2856	40	3

CONFIRMATION NO. 7781

23377
WOODCOCK WASHBURN LLP
CIRA CENTRE, 12TH FLOOR
2929 ARCH STREET
PHILADELPHIA, PA 19104-2891

FILING RECEIPT

OC000000051337996

Date Mailed: 12/19/2011

Receipt is acknowledged of this reissue patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Applicant(s)

Jeffrey A. Robl, ~~Residence Not Provided;~~ Newtown, PA (US)

Assignment For Published Patent Application

Bristol-Myers Squibb Company, Princeton, NJ

Power of Attorney: The patent practitioners associated with Customer Number 23377

Domestic Priority data as claimed by applicant

This application is a REI of 09/788,173 02/16/2001 PAT 6395767
which claims benefit of 60/188,555 03/10/2000

Foreign Applications (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.)

If Required, Foreign Filing License Granted: 12/06/2011

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/308,658**

Projected Publication Date: None, application is not eligible for pre-grant publication

Non-Publication Request: No

Early Publication Request: No

Richard B. Sulsky, West Trenton, NJ (US)
David J. Augeri, Princeton, NJ (US)
David R. Magnin, Hamilton, NJ (US)
Lawrence G. Hamann, Cherry Hill, NJ (US)
David A. Betebenner, Lawrenceville, NJ (US)

Title

Cyclopropyl-Fused Pyrrolidine-Based Inhibitors Of Dipeptidyl Peptidase IV And Method

Preliminary Class

514

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

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For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as

set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

Electronic Acknowledgement Receipt

EFS ID:	11748441
Application Number:	13308658
International Application Number:	
Confirmation Number:	7781
Title of Invention:	Cyclopropyl-Fused Pyrrolidine-Based Inhibitors Of Dipeptidyl Peptidase IV And Method
First Named Inventor/Applicant Name:	Jeffrey A. Robl
Customer Number:	23377
Filer:	SAMUEL VALLA/Ann Trevisani
Filer Authorized By:	SAMUEL VALLA
Attorney Docket Number:	BMS-2856
Receipt Date:	03-JAN-2012
Filing Date:	01-DEC-2011
Time Stamp:	16:04:30
Application Type:	Utility under 35 USC 111(a)

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	Request for Corrected Filing Receipt	Request_Corrected_Filing_Receipt.PDF	154027 4ed253dfeacd816928c1007f364a220cce48c52c	no	5

Warnings:	
Information:	

Total Files Size (in bytes):	154027

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

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United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
13/308,658	12/01/2011	1629	2950	BMS-2856	40	3

CONFIRMATION NO. 7781

CORRECTED FILING RECEIPT

23377
WOODCOCK WASHBURN LLP
CIRA CENTRE, 12TH FLOOR
2929 ARCH STREET
PHILADELPHIA, PA 19104-2891

OC000000051838602

Date Mailed: 01/06/2012

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Applicant(s)

Jeffrey A. Robl, Newtown, NJ;
Richard B. Sulsky, West Trenton, NJ;
David J. Augeri, Princeton, NJ;
David R. Magnin, Hamilton, NJ;
Lawrence G. Hamann, Cherry Hill, NJ;
David A. Betebenner, Lawrenceville, NJ;

Assignment For Published Patent Application

Bristol-Myers Squibb Company, Princeton, NJ

Power of Attorney: The patent practitioners associated with Customer Number 23377

Domestic Priority data as claimed by applicant

This application is a REI of 09/788,173 02/16/2001 PAT 6395767
which claims benefit of 60/188,555 03/10/2000

Foreign Applications (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.)

If Required, Foreign Filing License Granted: 12/06/2011

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/308,658**

Projected Publication Date: None, application is not eligible for pre-grant publication

Non-Publication Request: No

Early Publication Request: No

Title

Cyclopropyl-Fused Pyrrolidine-Based Inhibitors Of Dipeptidyl Peptidase IV And Method

Preliminary Class

514

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

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LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:
Jeffrey A. Robl et al.
Application No.: 13/308,658
Filing Date: December 1, 2011
Confirmation No.: 7781
Group Art Unit: 1629
Examiner:
For: Cyclopropyl-Fused Pyrrolidine-Based Inhibitors Of Dipeptidyl Peptidase IV and Method

Office of Initial Patent Examination
Customer Service Center
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR CORRECTED FILING RECEIPT

1. Attached is a copy of the corrected filing receipt issued by the U.S. Patent and Trademark Office on January 6, 2012 in connection with the above-referenced re-issue application for which issuance of a second corrected filing receipt is respectfully requested. The requested change is noted thereon, as well as listed below.

2. There is an error with respect to the residence of applicant Jeffrey A. Robl. Please see below:

   Incorrect Data: Jeffrey A. Robl, Newtown, NJ

   CORRECT DATA: Jeffrey A. Robl, Newtown, PA

Please charge any deficiency or credit any overpayment to Deposit Account No. 23-3050.

Date: January 9, 2012

/S. Maurice Valla/
S. Maurice Valla
Registration No. 43,966

Woodcock Washburn LLP
Cira Centre, 12th Floor
2929 Arch Street
Philadelphia, PA 19104-2891
Telephone: (215) 568-3100
Facsimile: (215) 568-3439

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
13/308,658	12/01/2011	1629	2950	BMS-2856	40	3

CONFIRMATION NO. 7781

CORRECTED FILING RECEIPT

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Early Publication Request: No

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Electronic Acknowledgement Receipt

EFS ID:	11789288
Application Number:	13308658
International Application Number:	
Confirmation Number:	7781
Title of Invention:	Cyclopropyl-Fused Pyrrolidine-Based Inhibitors Of Dipeptidyl Peptidase IV And Method
First Named Inventor/Applicant Name:	Jeffrey A. Robl
Customer Number:	23377
Filer:	SAMUEL VALLA/Ann Trevisani
Filer Authorized By:	SAMUEL VALLA
Attorney Docket Number:	BMS-2856
Receipt Date:	09-JAN-2012
Filing Date:	01-DEC-2011
Time Stamp:	14:49:53
Application Type:	Utility under 35 USC 111(a)

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	Request for Corrected Filing Receipt	Request_Corrected_Filing_Receipt.PDF	126803 8ae60b3d75f462f4f2a7a506e82e8a23227b25b7	no	5

Warnings:	
Information:	

Total Files Size (in bytes):	126803

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.

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
13/308,658	12/01/2011	1629	2950	BMS-2856	40	3

CONFIRMATION NO. 7781

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/308,658	12/01/2011	Jeffrey A. Robl	BMS-2856	7781

23377 7590 05/08/2012

WOODCOCK WASHBURN LLP
CIRA CENTRE, 12TH FLOOR
2929 ARCH STREET
PHILADELPHIA, PA 19104-2891

EXAMINER	
POLANSKY, GREGG	
ART UNIT	PAPER NUMBER
1629	

NOTIFICATION DATE	DELIVERY MODE
05/08/2012	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):

eofficemonitor@woodcock.com

Office Action Summary	Application No.	Applicant(s)	
	13/308,658	ROBL ET AL.	
	Examiner	Art Unit	
	Gregg Polansky	1629	

-- 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 *01 December 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) *1-22 and 25-40* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-22 and 25-40* is/are rejected.

8)☒ Claim(s) *38* 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 *12/01/2011*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 1-13 and 25-40 are pending.

2. By way of the submission filed on 12/01/2011, Applicants have canceled Claims 23 and 24, amended Claim 13, and added Claims 25-40.

Reissue Applications

3. Applicant is reminded of the continuing obligation under 37 CFR 1.178(b), to timely apprise the Office of any prior or concurrent proceeding in which Patent No. 6,395,767 is or was involved. These proceedings would include interferences, reissues, reexaminations, and litigation.

Applicant is further reminded of the continuing obligation under 37 CFR 1.56, to timely apprise the Office of any information which is material to patentability of the claims under consideration in this reissue application.

These obligations rest with each individual associated with the filing and prosecution of this application for reissue. See also MPEP §§ 1404, 1442.01 and 1442.04.

4. The reissue oath/declaration filed with this application is defective because it fails to identify at least one specific error which is relied upon to support the reissue application. See 37 CFR 1.175(a)(1) and MPEP § 1414.

Further, unless such information is supplied on an application data sheet in accordance with § 1.76, the oath or declaration must also identify the mailing address, and the residence if an inventor lives at a location which is different from where the

inventor customarily receives mail, of each inventor. The declaration presented did not give the mailing address and thus is defective.

It is suggested that Applicants use form PTO/SB/52 (Reissue Application Declaration By The Assignee) for preparing a the declaration.

Specification and Claim Objections

5. Changes to the Specification and Claims made Certificate of Correction to the original patent grant (Patent No. 6,395,767) have not been properly incorporated into the reissue patent. The applicant should include any changes, additions, or deletions that were made by a Certificate of Correction to the original patent grant in the reissue application without underlining or bracketing. Because these changes are retroactively a part of the original patent and are made before the reissue application will issue as a patent, they must show up in the printed reissue patent document as part of the original patent, i.e., not in italics or bracketed. See MPEP 1411.

When making the Certificate of Correction changes to the specification it is not called an amendment and the changes should be made without using underlining or brackets. Because the Certificate of Correction changes are retroactively a part of the original patent and are made before the reissue application will issue as a patent, they must show up in the printed reissue patent document as part of the original patent, i.e., not in italics or bracketed.

For example, to incorporate the following certificate of correction change:

Column 82,

Line 65, change “10EtOAc” to -- 10% EtOAc --.

Applicants would submit, for example, the following:

Certificate of Correction

Per the Certificate of Correction, please substitute the following paragraph for the paragraph at column 82, beginning at line 52:

According to literature (J. Org. Chem 1994, 59, 8215), a solution of Step 3 compound (0.875 g, 3.83 mmol) in dry benzene (4.0 mL) was treated with triethylamine (0.52 mL, 3.83 mmol) and diphenylphosphoryl azide (0.85 mL, 3.83 mmol), refluxed under nitrogen for 1 h and cooled to rt. The solution was treated with benzyl alcohol (0.60 mL, 5.75 mmol or 1.5 equiv), refluxed for 17 h, cooled then diluted with ether (40 mL). The solution was washed with 10% aqueous citric acid (2x3 mL), back-extracting the citric acid wash with ether (40 mL). The combined organic extracts were washed with 5% sodium bicarbonate (2x3 mL), dried (MgSO4), filtered, and concentrated. Flash chromatography on silica gel of the crude product with 10% EtOAc in hexane (1.0 L) gave step 4 compound as a clear thick syrup. Yield: 1.15 g (90%). MS(M+H) 334.

6. Claim 38 is objected to because of the following: The claim recites “The method of any one of claims 32, 33, 34, **25**, **26**, or 37, wherein… [emphasis added]”. The

recitation of “25” and “26” appears to be a typographical error and should be changed to “35” and “36”.

7. Claim 38 is objected to because of the following: The claim recites (at lines 5-6 of the claim) “an agent for preventing inhibiting allograft rejection in transplantation…” It appears that the word “or” should be between the words “preventing” and “inhibiting” (i.e. “preventing or inhibiting”).

Claim Rejections - 35 USC § 112

8. 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.

9. Claims 1-7, 11-22, 29-31 and 38-40 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.

Claim 1 is drawn to a compound having the Markush structure recited in the claim “**and** a pharmaceutically acceptable salt thereof…[emphasis added].” It is unclear whether the claim limitations are met by (or would be anticipated by) just a compound reading on the Markush structure (or, alternatively, a salt of the compound), or if the claim limitations are only met by (or would only be anticipated by) having both said compound and a salt of the compound. Thus, it is not possible to ascertain with reasonable precision when the claim is infringed and when it is not.

Claim 12 recites the limitation "a DP4 inhibitor compound as defined in claim 1". Similarly, Claim 22 recites “A pharmaceutical combination comprising a DP4 inhibitor

compound as defined in claim 1…" Claim 1 is drawn to a compound having the recited structure; Claim 1 does not define "a DP4 inhibitor compound". Thus, there is insufficient antecedent basis for this limitation in the claim. Claim 13, which depends from Claim 12, is similarly rejected.

Claim 17 contains parenthetical subject matter that renders the claim indefinite. The claim recites (at line 3 of the claim) "a serotonin (and dopamine) reuptake inhibitor…" It is not clear whether "and dopamine" in parentheses is a limitation or an option.

Claim 29 recites "The composition of claim 27 or 28 further comprising **another** antidiabetic agent other than a DP4 inhibitor [emphasis added]." Claims 27 and 28 (and the claims from which they depend) do not claim an "antidiabetic agent" and thus do not provide proper antecedence for "another antidiabetic agent".

As discussed above, Claim 38 recites "The method of any one of claims 32, 33, 34, **25**, **26**, or 37, wherein… [emphasis added]". The recitation of "25" and "26" appears to be a typographical error and should be changed to "35" and "36"; however, the claim must be examined as presently recited. Claims 25 and 26 are drawn to compounds and not to a method and thus do not provide proper antecedence for Claim 38.

10. 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.

11. Claims 1-7 and 11-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a Written Description rejection.

Claim 1 is drawn to a compound having the Markush structure recited in the claim "…or a prodrug ester thereof…." There is insufficient written basis in the Specification for prodrugs of the compounds recited in the claim.

Regarding the requirement for adequate written description of chemical entities, Applicants' attention is directed to MPEP §2163. In particular, *Regents of the University of California v. Eli Lilly & Co.,* 119 F.3d 1559, 1568 (Fed. Cir. 1997), *cert denied*, 523 U.S. 1089, 118 S. Ct. 1548 (1998), holds that an adequate written description requires a precise definition, such as by structure, formula, chemical name, or physical properties, "not a mere wish or plan for obtaining the claimed chemical invention." *Elli Liily*, 119 F.3d at 1566. The Federal Circuit has adopted the standard set forth in the Patent and Trademark Office ("PTO") Guidelines for Examination of Patent Applications under the 35 U.S.C. 112.1 "Written Description" Requirement ("Guidelines"), 66 Fed. Reg. 1099 (Jan. 5, 2001), which state that the written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics," including, *inter alia*, "functional characteristics when coupled with a known or disclosed correlation between function and structure…" *Enzo Biochem,*

Inc. v. Gen-Probe Inc., 296 F.3d 316, 1324-25 (Fed. Cir. 2002) (quoting *Guidelines*, 66 Fed. Reg. At 1106 (emphasis added)). Moreover, although *Elli Lilly* and *Enzo* were decided within the factual context of DNA sequences, this does not preclude extending the reasoning of those cases to chemical structures in general. *Univ. of Rochester v. G.D. Searle & Co.*, 249 Supp. 2d 216, 225 (W.D.N.Y. 2003).

Applicants have failed to provide any structural characteristics, chemical formula, name(s) or physical properties of prodrug esters of the claimed compounds, aside from a broad recitation that such are contemplated for use in the invention (see column 3, line 24 of the Specification). The Specification does not provide even a single example of a prodrug ester of any instant compound.

As such, it is not apparent that Applicant was actually in possession of, and intended to use within the context of the present invention, any specific prodrugs of the claimed compounds at the time the present invention was made. The skilled artisan could not "immediately envisage" the claimed compounds based on the description in the disclosure.

Conclusion

12. Claims 1-13 and 25-40 are rejected.

13. No claims are allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregg Polansky whose telephone number is (571)272-9070. The examiner can normally be reached on Mon-Thur 9:30 A.M. - 7:00 P.M. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey S. Lundgren can be reached on (571) 272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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.

/Gregg Polansky/
Examiner, Art Unit 1629

/JAMES D ANDERSON/
Primary Examiner, Art Unit 1629

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13308658	ROBL ET AL.
	Examiner	Art Unit
	GREGG POLANSKY	1629

✓	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

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Final	Original	05/01/2012								
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Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13308658	ROBL ET AL.
	Examiner	Art Unit
	GREGG POLANSKY	1629

✓	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	05/01/2012								
	37	✓								
	38	✓								
	39	✓								
	40	✓								

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13308658	ROBL ET AL.
	Examiner	Art Unit
	GREGG POLANSKY	1629

SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
EAST Search: see EAST Search Histroy	5/2/2012	GP
STN Search: see STN Search History	5/2/2012	GP
Litigation Search: see Litigation Search History	5/2/2012	GP
PALM Inventor Search	5/2/2012	GP

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

/GREGG POLANSKY/ Examiner.Art Unit 1629	

Substitute for 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	Not yet assigned
				Filing Date	Herewith
				First Named Inventor	Jeffrey A. Robl
				Art Unit	Not yet assigned
(use as many sheets as necessary)				**Examiner Name**	Not yet assigned
Sheet	1	of	2 ~~1~~	**Attorney Docket Number**	BMS-2856

U. S. PUBLICATION AND PATENT DOCUMENTS

Examiner Initials	Cite No.	Document Number Number – Kind Code (if known)	Publication or Grant Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document
	1	7,078,381	07-18-2006	Bachovchin et al.
	2	6,890,898	05-10-2005	Bachovchin et al.
	3	6,803,357	10-12-2004	Bachovchin et al.
	4	6,555,542	04-29-2003	O'Connor et al.
	5	5,561,146	10-01-1996	Kim et al.
	6	6,297,233	10-02-2001	Stein et al.
	7	4,255,334	03-10-1981	Day et al.
	8	6,060,432	05-09-2000	Adams et al.
	9	6,166,063	12-26-2000	Villhauer
	10	7,205,432	04-17-2007	Berner et al.
	11	7,250,529	07-31-2007	Williams
	12	3,325,478	06-13-1967	Hermann et al.
	13	3,906,044	09-16-1975	Aigami et al.
	14	2006/0287317	12-21-2006	Smith et al.

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Examiner Initials	Cite No.	Foreign Patent Document Country Code- Number - Kind Code (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	T
	15	WO 02/060894	08-08-2002	Bristol-Myers Squibb Co.	
	16	WO 00/47207	08-17-2000	Bristol-Myers Squibb Co.	
	17	WO 97/15576	05-01-1997	E.I. Du Pont de Nemours and Co.	
	18	EP 0686642	12-13-1995	Bristol-Myers Squibb Co.	
	19	DE 2521895	04-08-1976	Pliva Pharmazeutische and Chemische Fabrik	T
	20	DE 2449840	04-24-1975	Kao Soap Corp.	T

Examiner Signature		**Date Considered**	

Substitute for 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** *(use as many sheets as necessary)*				***Complete if Known***	
				Application Number	Not yet assigned
				Filing Date	Herewith
				First Named Inventor	Jeffrey A. Robl
				Art Unit	Not yet assigned
				Examiner Name	Not yet assigned
Sheet	2	of	2	**Attorney Docket Number**	BMS-2856

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials	Cite No.	Include name of the author, 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
	21	Hermann Stetter and Elli Rauscher, Zur Kenntnis der Adamantan-carbonsaure-(1) Chemische Berichte, 1960, vol. 93, no. 5, pp 1161-1166	T
	22	Von R. Hiltmann et al., "2-Acylaminopyridin-Derivate mit morphinagonistischer und antagonisterischer Wirksamkeit, Arzneimittel-Forschung," 1974, vol. 24, no. 4a, pp 584-600	T
	23	Peter Beak et al.," Intramolecular Cyclizations of alpha-Lithioamine Synthetic Equivalents: Convenient Synthesis of 3-, 5-, and 6-Membered Ring Heterocyclic Nitrogen Compounds and Elaborations of 3-Mimbered Ring Systems," J. Org. Chem. vol. 59, no. 2. 1994, pp 276-277.	
	24	David J. Augeri et al., "Discovery and Preclinical Profile of Saxagliptin (BMS-477118): A Highly Potent, Long-Acting, Orally Active Dipeptidyl Peptidase IV Inhibitor for the Treatment of Type 2 Diabetes," J. Med. Chem. 2005, 48, 5025-5037.	
	25	David R. Magnin et al. "Synthesis of Novel Potent Dipeptidyl Peptidase IV Inhibitors with Enhanced Chemical Stability: Interplay Between the N-Terminal Amino Acid Alkyl Side Chain and the Cyclopropyl Group of α-Aminoacyl-L-cis-4,5-methanoloprolinenitrile-Based Inhibitors," J. Med. Chem. 2004, 47, 2587-2598.	

Examiner Signature	/Gregg Polansky/	**Date Considered**	04/30/2012

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CONFIRMATION NO. 7781

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
13/308,658	12/01/2011	514	1629	BMS-2856

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Lawrence G. Hamann, Cherry Hill, NJ;
David A. Betebenner, Lawrenceville, NJ;

**** CONTINUING DATA ***************************

This application is a REI of 09/788,173 02/16/2001 PAT 6,395,767
which claims benefit of 60/188,555 03/10/2000

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****

12/06/2011

Foreign Priority claimed ☐ Yes ☑ No 35 USC 119(a-d) conditions met ☐ Yes ☑ No Verified and Acknowledged /GREGG POLANSKY/ Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		PA		40	3

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PHILADELPHIA, PA 19104-2891
UNITED STATES

TITLE

Cyclopropyl-Fused Pyrrolidine-Based Inhibitors Of Dipeptidyl Peptidase IV And Method

FILING FEE RECEIVED		
2950	FEES: Authority has been given in Paper 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)

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S5	339	BMS-477118	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	AND	ON	2012/04/30 15:39
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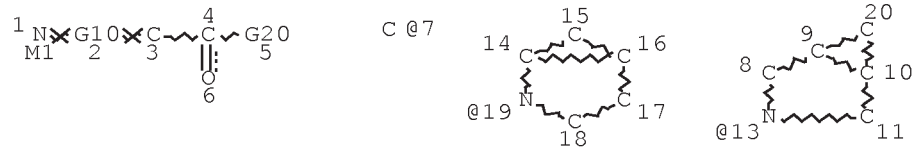


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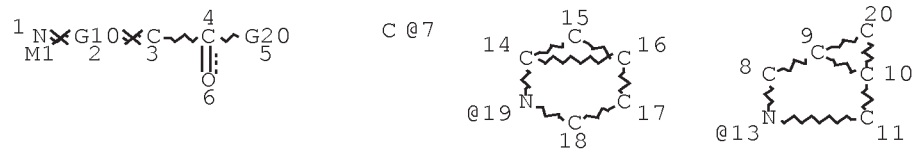


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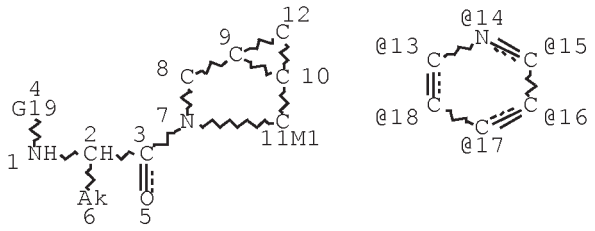

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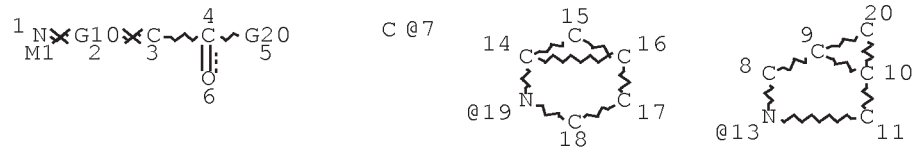

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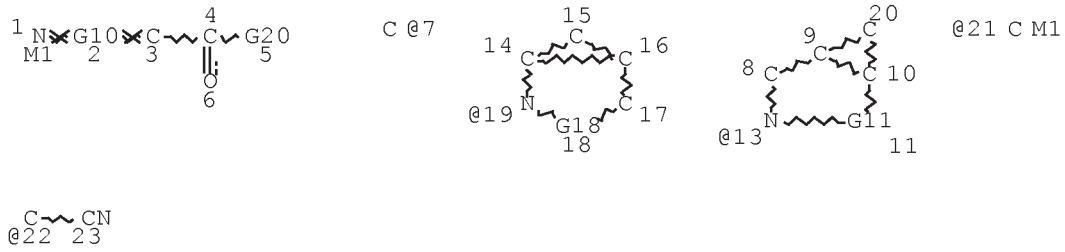

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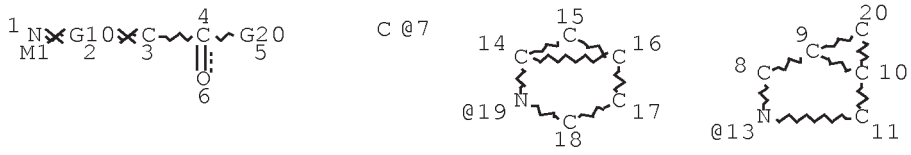

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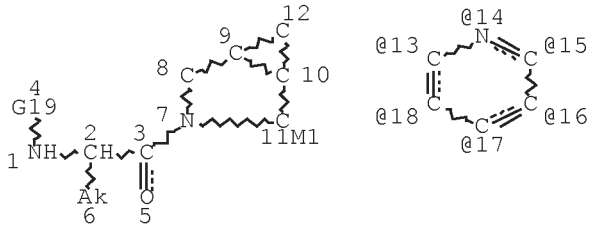

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NUMBER OF NODES IS 18

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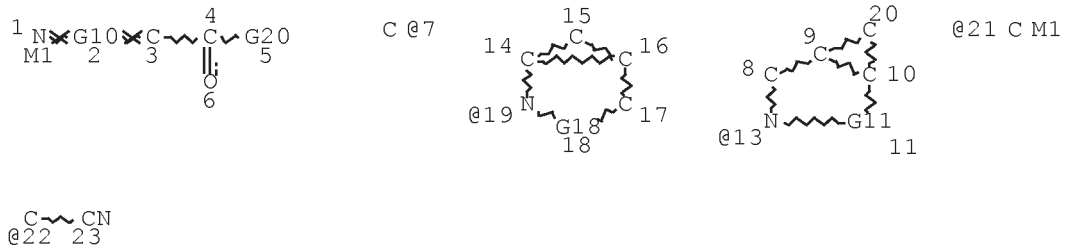
L20 STR




```
REP G10=(0-1) 7
VAR G11=21/22
VAR G18=21/22
VAR G20=13/19
NODE ATTRIBUTES:
HCOUNT  IS M1     AT   1
HCOUNT  IS M1     AT  21
NSPEC   IS RC     AT   1
NSPEC   IS RC     AT   3
NSPEC   IS RC     AT   7
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC  14  13
NUMBER OF NODES IS  22

STEREO ATTRIBUTES: NONE
L22        8057 SEA FILE=REGISTRY SUB=L14 SSS FUL L20
L23        8053 SEA FILE=REGISTRY SPE=ON  ABB=ON  PLU=ON  L22 NOT L19


=> d que stat l41
L12             STR
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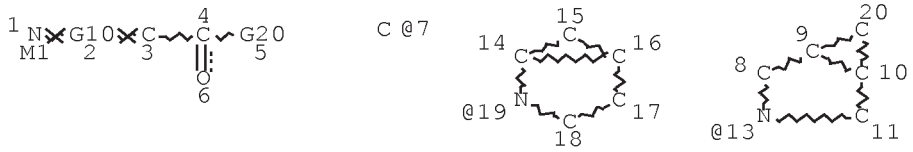


```
REP G10=(0-1) 7
VAR G20=13/19
NODE ATTRIBUTES:
HCOUNT  IS M1     AT   1
NSPEC   IS RC     AT   1
NSPEC   IS RC     AT   3
NSPEC   IS RC     AT   7
DEFAULT MLEVEL IS ATOM
```

DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC 14 13
NUMBER OF NODES IS 19

STEREO ATTRIBUTES: NONE
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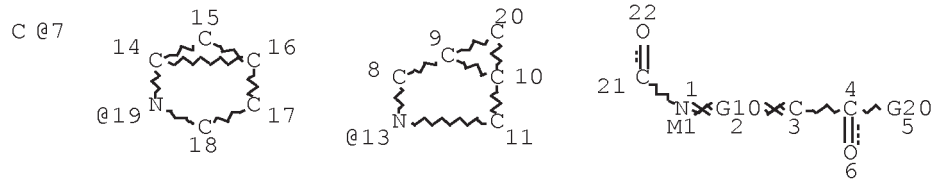
L39   STR



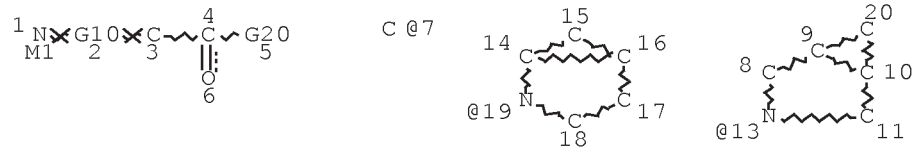
REP G10=(0-1) 7
VAR G20=13/19
NODE ATTRIBUTES:
HCOUNT IS M1   AT   1
NSPEC   IS RC   AT   1
NSPEC   IS RC   AT   3
NSPEC   IS RC   AT   7
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC 14 13
NUMBER OF NODES IS 21

STEREO ATTRIBUTES: NONE
L41   6632 SEA FILE=REGISTRY SUB=L14 SSS FUL L39

100.0% PROCESSED   7896 ITERATIONS   6632 ANSWERS
SEARCH TIME: 00.00.01

=> d que stat l42
L12   STR



REP G10=(0-1) 7

VAR G20=13/19
NODE ATTRIBUTES:
HCOUNT IS M1 AT 1
NSPEC IS RC AT 1
NSPEC IS RC AT 3
NSPEC IS RC AT 7
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC 14 13
NUMBER OF NODES IS 19

STEREO ATTRIBUTES: NONE
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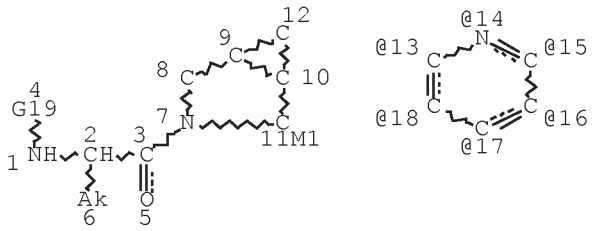
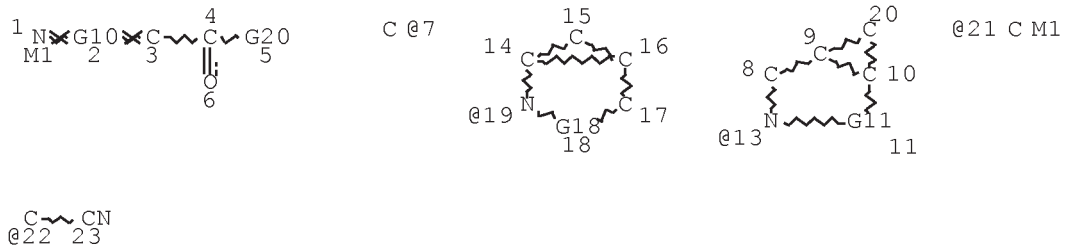
L17 STR



VAR G19=13/14/15/16/17/18
NODE ATTRIBUTES:
HCOUNT IS M1 AT 11
CONNECT IS E1 RC AT 6
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 18

STEREO ATTRIBUTES: NONE
L19 4 SEA FILE=REGISTRY SUB=L14 SSS FUL L17
L20 STR



```
REP G10=(0-1) 7
VAR G11=21/22
VAR G18=21/22
VAR G20=13/19
NODE ATTRIBUTES:
HCOUNT  IS M1     AT   1
HCOUNT  IS M1     AT  21
NSPEC   IS RC     AT   1
NSPEC   IS RC     AT   3
NSPEC   IS RC     AT   7
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC  14  13
NUMBER OF NODES IS  22

STEREO ATTRIBUTES: NONE
L22         8057 SEA FILE=REGISTRY SUB=L14 SSS FUL L20
L23         8053 SEA FILE=REGISTRY SPE=ON  ABB=ON  PLU=ON  L22 NOT L19
L39              STR
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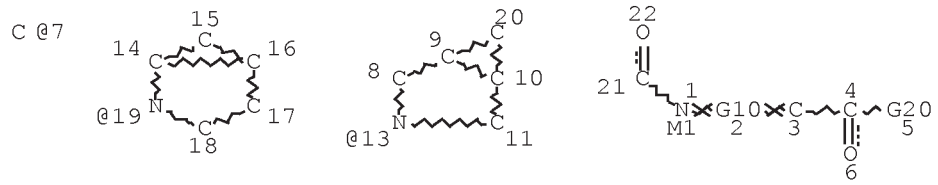
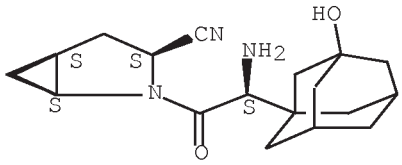



```
REP G10=(0-1) 7
VAR G20=13/19
NODE ATTRIBUTES:
HCOUNT  IS M1     AT   1
NSPEC   IS RC     AT   1
NSPEC   IS RC     AT   3
NSPEC   IS RC     AT   7
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC  14  13
NUMBER OF NODES IS  21

STEREO ATTRIBUTES: NONE
L41         6632 SEA FILE=REGISTRY SUB=L14 SSS FUL L39
L42         1421 SEA FILE=REGISTRY SPE=ON  ABB=ON  PLU=ON  L23 NOT L41


=> d que nos l49
L1             1 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  US2001-788173/APPS
L12              STR
```

```
L14         8057 SEA FILE=REGISTRY SSS FUL L12
L17              STR
L19            4 SEA FILE=REGISTRY SUB=L14 SSS FUL L17
L20              STR
L22         8057 SEA FILE=REGISTRY SUB=L14 SSS FUL L20
L23         8053 SEA FILE=REGISTRY SPE=ON  ABB=ON  PLU=ON  L22 NOT L19
L24              QUE  SPE=ON  ABB=ON  PLU=ON  ROBL, J?/AU,AUTH,IN
L25              QUE  SPE=ON  ABB=ON  PLU=ON  SULSKY, R?/AU,AUTH,IN
L26              QUE  SPE=ON  ABB=ON  PLU=ON  SULSKY, D?/AU,AUTH,IN
L27              QUE  SPE=ON  ABB=ON  PLU=ON  AUGERI, D?/AU,AUTH,IN
L28              QUE  SPE=ON  ABB=ON  PLU=ON  MAGNIN, D?/AU,AUTH,IN
L29              QUE  SPE=ON  ABB=ON  PLU=ON  HAMANN, L?/AU,AUTH,IN
L30              QUE  SPE=ON  ABB=ON  PLU=ON  BETEBENNER, D?/AU,AUTH,IN
L32              QUE  SPE=ON  ABB=ON  PLU=ON  AY<2001 OR PY<2001 OR PRY<20
                 01 OR MY<2001 OR REVIEW/DT
L39              STR
L41         6632 SEA FILE=REGISTRY SUB=L14 SSS FUL L39
L42         1421 SEA FILE=REGISTRY SPE=ON  ABB=ON  PLU=ON  L23 NOT L41
L44          427 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  L42
L45           15 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  L44 AND (L24 OR L25
                 OR L26 OR L27 OR L28 OR L29 OR L30)
L46            0 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  L1 NOT L45
L47           15 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  (L45 OR L46)
L48          412 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  L44 NOT L47
L49           87 SEA FILE=HCAPLUS SPE=ON  ABB=ON  PLU=ON  L48 AND L32
```

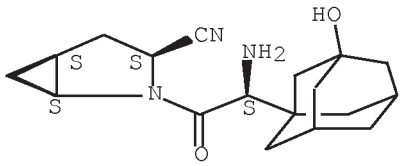
```
=> d l49 ibib ed abs hitstr 1-30
YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS' - CONTINUE? (Y)/N:y



L49  ANSWER 1 OF 87  HCAPLUS  COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER:        2012:307629  HCAPLUS  Full-text
DOCUMENT NUMBER:         156:327731
TITLE:                   DPP-4 inhibitors in the treatment of type 2 diabetes
AUTHOR(S):               Duez, Helene; Cariou, Bertrand; Staels, Bart
CORPORATE SOURCE:        Univ Lille Nord de France, Lille, F-59000, Fr.
SOURCE:                  Biochemical Pharmacology (2012), 83(7), 823-832
                         CODEN: BCPCA6; ISSN: 0006-2952
PUBLISHER:               Elsevier B.V.
DOCUMENT TYPE:           Journal; General Review; (online computer file)
LANGUAGE:                English
ED   Entered STN:  02 Mar 2012
AB    A review.  Although being a primary objective in the management of type 2
      diabetes, optimal glycemic control is difficult to achieve and usually not
      maintained over time.  Type 2 diabetes is a complex pathol., comprising
      altered insulin sensitivity and impaired insulin secretion.  Recent
      advances in the understanding of the physiol. functions of incretins and
      their degrading enzyme dipeptidyl-peptidase (DPP)-4 have led to the
      discovery' of a new class of oral anti-diabetic drugs.  Several DPP-4
      inhibitors (or gliptins) with different chemical structures are now
      available.  These agents inhibit the degradation of the incretins
      glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic
      polypeptide (GIP) and hence potentiate glucose-dependent insulin secretion.
      DPP-4 inhibitors inhibit DPP-4 activity by almost 100% in vitro, maintaining
      a ≥80% inhibition throughout the treatment period in vivo, thus prolonging
      GLP-1 half-life, and significantly reducing HbA1c generally by -0.7 to 0.8%
      as well as fasting and post-prandial glycemia.  They are well-tolerated with
      no weight gain and few adverse effects, and, of particular interest, no
      increase in hypoglycemic episodes.  Although different by their chemical
      structure and pharmacokinetic properties, the DPP4 inhibitors currently
      available have proven similar glucose lowering efficacy.
IT   361442-04-8, Saxagliptin
     RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
     (Biological study); USES (Uses)
        (DPP-4 inhibitors in treatment of type 2 diabetes)
RN   361442-04-8  HCAPLUS
CN   2-Azabicyclo[3.1.0]hexane-3-carbonitrile,
     2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-,
     (1S,3S,5S)-  (CA INDEX NAME)

Absolute stereochemistry.
```



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 107 THERE ARE 107 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

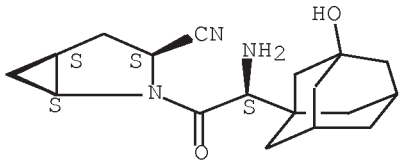
L49 ANSWER 2 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2012:21882 HCAPLUS Full-text
TITLE: Pharmacological and clinical evaluations of a new drug on treating type 2 diabetes:saxagliptin
AUTHOR(S): Lu, Ju-ming
CORPORATE SOURCE: Department of Endocrionology, Chinese PLA General Hospital, Beijing, 100853, Peop. Rep. China
SOURCE: Zhongguo Xinyao Zazhi (2011), 20(21), 2039-2043
CODEN: ZXZHA6; ISSN: 1003-3734
PUBLISHER: Zhongguo Xinyao Zazhi Youxian Gongsi
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Chinese
ED Entered STN: 05 Jan 2012
AB This review with 28 refs. summarizes the action mechanisms, pharmacokinetics, clin. studies and adverse reactions of saxagliptin as a therapeutic drug with new action mechanisms for treating type 2 diabetes.
IT INDEXING IN PROGRESS
IT 361442-04-8, Saxagliptin
RL: DMA (Drug mechanism of action); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmacol. and clin. evaluations of saxagliptin on treating type 2 diabetes)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



L49 ANSWER 3 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2011:1662838 HCAPLUS Full-text
TITLE: Medicinal chemistry and applications of incretins and DPP-4 inhibitors in the treatment of Type 2 diabetes mellitus
AUTHOR(S): Lotfy, Mohamed; Singh, Jaipaul; Kalasz, Huba; Tekes, Kornelia; Adeghate, Ernest
CORPORATE SOURCE: Department of Biology, Faculty of Science, UAE University, Al Ain, United Arab Emirates
SOURCE: Open Medicinal Chemistry Journal (2011), 5, 82-92
CODEN: OMCJB6; ISSN: 1874-1045
PUBLISHER: Bentham Science Publishers Ltd.
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English
ED Entered STN: 27 Dec 2011
AB Diabetes mellitus (DM) is a major metabolic disorder currently affecting over 200 million people worldwide. Approx. 90% of all diabetic patients suffer from Type 2 diabetes mellitus (T2DM). The world's economy coughs out billions of dollars annually to diagnose, treat and manage patients with diabetes. It has been shown that the naturally occurring gut hormones incretins, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) can preserve the morphol. and function of pancreatic beta cell. In addition, GIP and GLP-1 act on insulin receptors to facilitate insulin-receptor binding, resulting in optimal glucose metabolism This review examines the medicinal chemical and roles of incretins, specifically, GLP-1 and drugs which can mimic its actions and prevent its enzymic degradation The review discussed GLP-1 agonists such as exenatide, liraglutide, taspoglutide and albiglutide. The paper also identified and reviewed a number of inhibitors, which can block dipeptidyl peptidase 4 (DPP-4), the enzyme responsible for the rapid degradation of GLP-1. These DPP-4 inhibitors include sitagliptin, saxagliptin, vildagliptin and many others which are still in the exptl. phase.
IT INDEXING IN PROGRESS
IT 361442-04-8, Saxagliptin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(medicinal chemical and applications of incretins and dipeptidyl peptidase
4 inhibitors in the treatment of type 2 diabetes mellitus)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

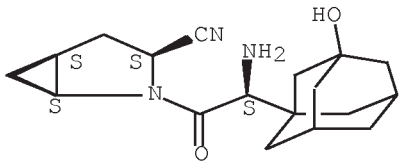
Absolute stereochemistry.



REFERENCE COUNT: 124 THERE ARE 124 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 4 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2011:1607699 HCAPLUS Full-text
TITLE: A review of gliptins in 2011
AUTHOR(S): Scheen, Andre J.
CORPORATE SOURCE: Division of Diabetes, Nutrition and Metabolic Disorders, and Division of Clinical Pharmacology, Department of Medicine, University of Liege, CHU Sart Tilman (B35), Liege, B-4000, Belg.
SOURCE: Expert Opinion on Pharmacotherapy (2012), 13(1), 81-99
CODEN: EOPHF7; ISSN: 1465-6566
PUBLISHER: Informa Healthcare
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English
ED Entered STN: 14 Dec 2011
AB Introduction: Dipeptidylpeptidase-4 (DPP-4) inhibitors offer new options for the management of type 2 diabetes (T2DM).Areas covered: This paper is an updated review, providing an anal. of both the similarities and the differences between the various compds. known as gliptins, currently used in the clinic (sitagliptin, vildagliptin, saxagliptin, alogliptin and linagliptin). This paper discusses the pharmacokinetic and pharmacodynamic characteristics of gliptins; both the efficacy and safety profiles of gliptins in clin. trials (compared with classical glucose-lowering agents), given as monotherapy or in combination, including in special populations; the positioning of DPP-4 inhibitors in the management of T2DM in recent guidelines; and various unanswered questions and perspectives.Expert opinion: The role of DPP-4 inhibitors in the therapeutic armamentarium of T2DM is evolving, as their potential strengths and weaknesses become better defined. Future critical issues may include the durability of glucose control, resulting from better β-cell protection, pos. effects on cardiovascular outcomes and long-term safety issues.
IT INDEXING IN PROGRESS
IT 361442-04-8, Saxagliptin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(sitagliptin, vildagliptin, saxagliptin, alogliptin and linagliptin may be safe, effective and may show favorable pharmacokinetic and pharmacodynamic characteristics in patient with type 2 diabetes)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)
REFERENCE COUNT: 136 THERE ARE 136 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

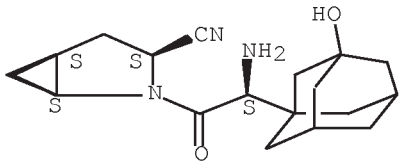
L49 ANSWER 5 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2011:1607697 HCAPLUS Full-text
TITLE: Metformin + saxagliptin for type 2 diabetes
AUTHOR(S): Scheen, Andre J.
CORPORATE SOURCE: Department of Medicine, Division of Diabetes, Nutrition and Metabolic Disorders, and Division of Clinical Pharmacology, University of Liege, CHU Sart Tilman (B35), Liege, B-4000, Belg.
SOURCE: Expert Opinion on Pharmacotherapy (2012), 13(1), 139-146
CODEN: EOPHF7; ISSN: 1465-6566
PUBLISHER: Informa Healthcare
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English
ED Entered STN: 14 Dec 2011
AB Introduction: Metformin is considered as the first-line drug therapy for the management of type 2 diabetes. Dipeptidyl peptidase-4 (DPP-4) inhibitors, by promoting insulin secretion and reducing glucagon secretion in a glucose-dependent manner, offer new opportunities for oral therapy after failure of metformin.Areas covered: An updated review of the literature demonstrates that saxagliptin, a DPP-4 inhibitor, and metformin may be administered together, sep. or in fixed-dose combination (FDC), either as saxagliptin added to metformin or as initial combination in drug-naive patients. Both compds. exert complementary pharmacodynamic actions leading to better improvement in blood glucose control (fasting plasma glucose, postprandial glucose, HbA1c) than either compound sep. Adding saxagliptin to metformin monthotherapy results in a consistent, sustained and safe reduction in HbA1c levels. Tolerance is excellent without hypoglycemia or weight gain.Expert opinion: The combination saxaglitpin plus metformin may be used as first-line or second-line therapy in the management of type 2 diabetes, especially as a valuable alternative to the classical metformin-sulfonylurea combination.
IT INDEXING IN PROGRESS
IT 361442-04-8, Saxagliptin
RL: BSU (Biological study, unclassified); BIOL (Biological study)

(metformin plus saxagliptin exerted complementary pharmacodynamic actions leading to better improvement in fasting plasma glucose, postprandial glucose and glycated Hb in patient with type 2 diabetes)

RN 361442-04-8 HCAPLUS

CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 6 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN

ACCESSION NUMBER: 2011:1569695 HCAPLUS Full-text

TITLE: Saxagliptin: a dipeptidyl peptidase-4 inhibitor in the treatment of type 2 diabetes mellitus

AUTHOR(S): Dave, Darshan J.

CORPORATE SOURCE: Department of Pharmacology, P.D.U. Medical College, Rajkot, 360 001, India

SOURCE: Journal of Pharmacology and Pharmacotherapeutics (2011), 2(4), 230-235
CODEN: JPPOGN; ISSN: 0976-500X

PUBLISHER: Medknow Publications and Media Pvt. Ltd.

DOCUMENT TYPE: Journal; General Review; (online computer file)

LANGUAGE: English

ED Entered STN: 07 Dec 2011

AB Type 2 diabetes mellitus (T2DM) is a metabolic disorder characterized by insulin deficiency or resistance. Management starts with single oral antidiabetic drug (OAD) but eventually switch over to combination therapy because of progressive β-cell dysfunction. Hypoglycemia, weight gain, and adverse cardiovascular events are major limitations of the available OADs (Sulfonylureas [SUs], thiazolidinediones [TZDs]). Saxagliptin, a reversible, competitive dipeptidyl peptidase-4 inhibitor, is recently approved agent in the treatment of T2DM. It acts by preventing the degradation of glucagon-like peptide-1 and hence increases secretion of insulin and decreases secretion of glucagon. It is a well-tolerated agent with commonly reported adverse events which include upper respiratory tract infection, urinary tract infection, and headache. Hypoglycemia, weight gain, and adverse cardiovascular events are negligible as compared with other OADs. In clin. studies, saxagliptin was found to be effective and well tolerated when used as a monotherapy as well as in combination with metformin,

SUs and TZDs. It is administered in the dose range of 2.5 to 5 mg once a day regardless of meal. Dosage reduction is required in patients having moderate to severe renal impairment as well as with concurrent administration of strong CYP3A4/5 inhibitors. To conclude, saxagliptin because of its novel mechanism of action (preserving beta cell function) and better tolerability profile seems to be a promising agent in the treatment of T2DM, especially in the early stage of the disease, but long-term clin. studies are required to prove its status in the management of T2DM.

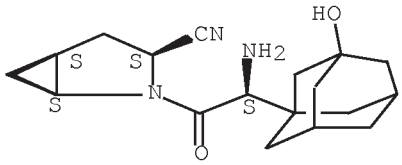
IT INDEXING IN PROGRESS

IT 361442-04-8, Saxagliptin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(dipeptidyl peptidase-4 inhibitor saxagliptin was well tolerated and effective as monotherapy or as combination therapy with oral antidiabetic drugs in patient with type 2 diabetes mellitus)

RN 361442-04-8 HCAPLUS

CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 7 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN

ACCESSION NUMBER: 2011:1506904 HCAPLUS Full-text

TITLE: Tolerability of Dipeptidyl Peptidase-4 Inhibitors: A Review

AUTHOR(S): Richard, Kathleen R.; Shelburne, Jamie S.; Kirk, Julienne K.

CORPORATE SOURCE: Wake Forest School of Medicine, Winston-Salem, NC, USA

SOURCE: Clinical Therapeutics (2011), 33(11), 1609-1629
CODEN: CLTHDG; ISSN: 0149-2918

PUBLISHER: Elsevier

DOCUMENT TYPE: Journal; General Review; (online computer file)

LANGUAGE: English

ED Entered STN: 24 Nov 2011

AB Background: Oral glucose-lowering agents are used to treat patients with type 2 diabetes mellitus (T2DM). Most patients require multiple agents to maintain glycemic targets. Dipeptidyl peptidase-4 (DPP-4) inhibitors are administered as monotherapy and in combination therapy for the treatment of T2DM. Objective: The aim of this article was to provide a thorough review of published tolerability data on 5 DPP-4 inhibitors. Methods: PubMed and Web of Science were searched for English-language clin. trials published from

Jan. 2000 to June 2001, using the following key words: dipeptidyl peptidase-4 inhibitor, vildagliptin, alogliptin, sitagliptin, saxagliptin, linagliptin, safety, tolerability, efficacy, effect, AE, and adverse effect. Studies were considered for inclusion if they were randomized, double-blind trials performed in patients ≥18 years of age with T2DM and with a Hb A1c of ≥6.5%; included ≥1 arm that received monotherapy with DPP-4; and reported adverse events (AEs). Studies in patients with a history of type 1 or secondary forms of diabetes, significant diabetic complications or cardiovascular disease within the 6 mo before the start of the study, hepatic disease or abnormalities, and/or renal abnormalities were excluded. Results: A total of 45 clin. trials, 5 pharmacokinetic studies, and 28 meta-analyses or reviews were included. The duration of studies ranged from 7 days to 104 wk. The most commonly reported AEs were nasopharyngitis, upper respiratory infections, all-cause infections, headache, gastrointestinal symptoms, and musculoskeletal pain. Based on the findings from the studies, the DPP-4 inhibitors had minimal impact on weight and were not associated with an increased risk for hypoglycemia relative to placebo. Rates of nasopharyngitis were higher with the DDP-4 inhibitors than with placebo. Pancreatitis was reported at lower rates with the DPP-4 inhibitors compared with other oral antihyperglycemic agents. Cardiovascular events were limited, and postmarketing studies are ongoing. Conclusions: The tolerability of DPP-4 inhibitors is supported by published clin. trials. The rates of weight gain, gastrointestinal AEs, and hypoglycemia were minimal with the DPP-4 inhibitors studied.

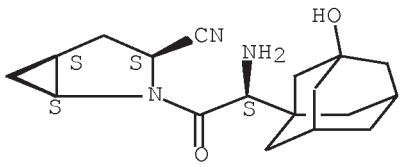
IT INDEXING IN PROGRESS

IT 361442-04-8, Saxagliptin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(tolerability of dipeptidyl peptidase-4 inhibitors)

RN 361442-04-8 HCAPLUS

CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 84 THERE ARE 84 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 8 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN

ACCESSION NUMBER: 2011:1489656 HCAPLUS Full-text

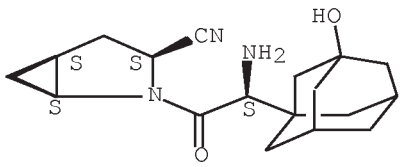
TITLE: Choosing a gliptin

AUTHOR(S): Gupta, Vishal; Kalra, Sanjay

CORPORATE SOURCE: Department of Endocrinology, Jaslok Hospital and

Research Centre, Mumbai, 400026, India
SOURCE: Indian Journal of Endocrinology and Metabolism (2011), 15(4), 298-308
CODEN: IJEMGB; ISSN: 2230-9500
PUBLISHER: Medknow Publications and Media Pvt. Ltd.
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English
ED Entered STN: 22 Nov 2011
AB The treatment of type 2 diabetes mellitus (T2DM) has included the use of metformin and sulfonylurea (SU) as first-line anti-diabetic therapies world over since years. This remains, despite the knowledge that the combination results in a progressive decline in [beta]-cell function and by 3 years up to 50% of diabetic patients can require an addnl. pharmacol. agent to maintain the glycosylated Hb (HbA1c) <7.0% (UKPDS). Gliptins represent a novel class of agents that improve beta cell health and suppress glucagon, resulting in improved post-prandial and fasting hyperglycemia. They function by augmenting the incretin system (GLP-1 and GIP) preventing their metabolism by dipeptidyl peptidase-4 (DPP-4). Not only are they efficacious but also safe (weight neutral) and do not cause significant hypoglycemia, making it a unique class of drugs. This review focuses on gliptins (sitagliptin, vildagliptin, saxagliptin, linagliptin and alogliptin) discussing pharmacokinetics, pharmacodynamics, efficacy and safety.
IT INDEXING IN PROGRESS
IT 361442-04-8, Saxagliptin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(saxagliptin was safe and effective in treatment of patient with type 2 diabetes mellitus)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.

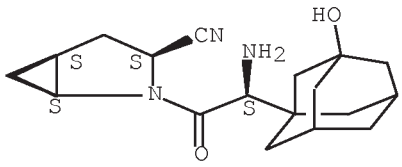


REFERENCE COUNT: 97 THERE ARE 97 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 9 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2011:1292912 HCAPLUS Full-text
TITLE: Linagliptin and newer DPP-4 inhibitors: newer uses and newer indications
AUTHOR(S): Kalra, Sanjay; Unnikrishnan, Ambika G.; Agrawal, Navneet; Singh, Anupam K.
CORPORATE SOURCE: Bharti Hospital, Karnal, India

SOURCE: Recent Patents on Endocrine, Metabolic & Immune Drug Discovery (2011), 5(3), 197-202
CODEN: RPEMBB; ISSN: 1872-2148
PUBLISHER: Bentham Science Publishers Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 12 Oct 2011
AB The dipeptidyl peptidase-4 (DPP-4) inhibitors linagliptin, sitagliptin, saxagliptin, vildagliptin and alogliptin are being developed and have been approved for the treatment of type-2 diabetes. These agents may be used either as monotherapy for the treatment of type-2 diabetes or in combination with other anti-diabetic drugs. The present review highlights the use of linagliptin and other new (DPP-4) inhibitors in the management of type-2 diabetes. The review also highlights advantages, comparative pharmacokinetic, safety profile and other potential uses including potential newer indications of DPP-4 inhibitors and relevant patents. The other potential uses that are not restricted to diabetes include obesity, cardiovascular disease, neurol. disease, hepatobiliary disease, wound healing, and other inflammatory illnesses.
IT INDEXING IN PROGRESS
IT 361442-04-8, Saxagliptin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(uses and new indications of linagliptin and newer DPP-4 inhibitors)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.

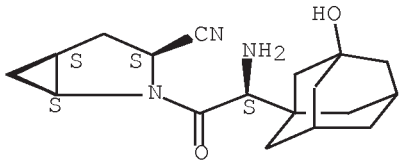


OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 10 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2011:1255500 HCAPLUS Full-text
TITLE: Pharmacology of dipeptidyl peptidase-4 inhibitors:similarities and differences
AUTHOR(S): Baetta, Roberta; Corsini, Alberto
CORPORATE SOURCE: Department of Pharmacological Sciences, University of Milan, Milan, Italy
SOURCE: Drugs (2011), 71(11), 1441-1467
CODEN: DRUGAY; ISSN: 0012-6667

PUBLISHER: Adis Data Information BV
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 04 Oct 2011
AB The dipeptidyl peptidase (DPP)-4 inhibitors, which enhance glucose-dependent insulin secretion from pancreatic β cells by preventing DPP-4-mediated degradation of endogenously released incretin hormones, represent a new therapeutic approach to the management of type 2 diabetes mellitus. The 'first-in-class' DPP-4 inhibitor, sitagliptin, was approved in 2006; it was followed by vildagliptin (available in the EU and many other countries since 2007, although approval in the US is still pending), saxagliptin (in 2009), alogliptin (in 2010, presently only in Japan) and linagliptin, which was approved in the US in May 2011 and is undergoing regulatory review in Japan and the EU. As the number of DPP-4 inhibitors on the market increases, potential differences among the different members of the class become important when deciding which agent is best suited for an individual patient. The aim of this review is to provide a comprehensive and updated comparison of the pharmacodynamic and pharmacokinetic properties of DPP-4 inhibitors, and to pinpoint pharmacol. differences of potential interest for their use in therapy. Despite their common mechanism of action, these agents show significant structural heterogeneity that could translate into different pharmacol. properties. At the pharmacokinetic level, DPP-4 inhibitors have important differences, including half-life, systemic exposure, bioavailability, protein binding, metabolism, presence of active metabolites and excretion routes. These differences could be relevant, especially in patients with renal or hepatic impairment, and when considering combination therapy. At the pharmacodynamic level, the data available so far indicate a similar glucose-lowering efficacy of DPP-4 inhibitors, either as monotherapy or in combination with other hypoglycemic drugs, a similar weight-neutral effect, and a comparable safety and tolerability profile. Data on nonglycemic parameters are scant at present and do not allow a comparison among DPP-4 inhibitors. Several phase III trials of DPP-4 inhibitors are currently ongoing; these trials, along with post-marketing surveillance data, will hopefully increase our knowledge about the long-term efficacy and safety of DPP-4 inhibitor therapy, the effect on pancreatic cell function and peripheral glucose metabolism, and the effect on cardiovascular outcomes in patients with type 2 diabetes.
IT INDEXING IN PROGRESS
IT 361442-04-8, Saxagliptin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(pharmacol. of dipeptidyl peptidase-4 inhibitors)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile,
2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-,
(1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.

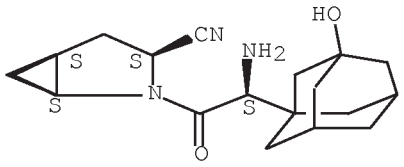


OS.CITING REF COUNT: 6 THERE ARE 6 CAPLUS RECORDS THAT CITE THIS RECORD (7 CITINGS)
REFERENCE COUNT: 166 THERE ARE 166 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 11 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2011:1006450 HCAPLUS Full-text
DOCUMENT NUMBER: 155:398157
TITLE: Patient considerations and clinical utility of a fixed dose combination of saxagliptin/metformin in the treatment of type 2 diabetes
AUTHOR(S): Derosa, Giuseppe; Maffioli, Pamela
CORPORATE SOURCE: Department of Internal Medicine and Therapeutics, University of Pavia, Pavia, Italy
SOURCE: Diabetes, Metabolic Syndrome and Obesity (2011), 4, 263-271
CODEN: DMSOAD; ISSN: 1178-7007
URL: http://www.dovepress.com/getfile.php?fileID=10436
PUBLISHER: Dove Medical Press Ltd.
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English
ED Entered STN: 14 Aug 2011
AB A review. Introduction: Targeting glycated Hb (HbA1c) levels below 7.0% is considered a primary goal of diabetes care, given its importance in obtaining a sustained reduction in microvascular and possibly macrovascular complications. Aim: The aim of this review was to evaluate the clin. utility of a fixed dose combination of saxagliptin/metformin in the treatment of type 2 diabetes. Evidence Review: The combination of saxagliptin/metformin was well tolerated and produced sustained glycemic control for up to 76 wk, with greater improvements in glycemic parameters compared with either drug alone. The saxagliptin/metformin combination also proved its non-inferiority compared with either sulfonylurea/metformin or sitagliptin/metformin combinations. Place in Therapy: Clin. practice recommends lifestyle interventions together with starting metformin at the time that the type 2 diabetes mellitus is diagnosed. Once metformin fails to maintain glycemic control, the addition of DPP-4 inhibitors should be the logical choice because of their effects on HbA1c compared to the addition of a sulfonylurea or glitazone and because of their pos. effects on beta cell function and their neutral effects on body weight Furthermore, DPP-4 inhibitors prevent the risk of hypoglycemia posed by sulfonylureas.
IT 361442-04-8, Saxagliptin
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity);

THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(patient considerations and clin. utility of fixed dose combination of saxagliptin/metformin in treatment of type 2 diabetes)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.

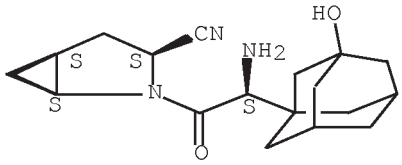


OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)
REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 12 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2011:938884 HCAPLUS Full-text
DOCUMENT NUMBER: 156:378948
TITLE: Comment on Gerich - DPP-4 inhibitors: What may be the clinical differentiators?
AUTHOR(S): Chen, Roland; Oehman, Peter; Kirby, Mark
CORPORATE SOURCE: Bristol-Myers Squibb, Princeton, NJ, 08543, USA
SOURCE: Diabetes Research and Clinical Practice (2011), 93(1), e3-e4
CODEN: DRCPE9; ISSN: 0168-8227
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 28 Jul 2011
AB A review. A polemic in response to Gerich (Diabetes Res. Clin. Pract. 2010; 90: 131-140), who summarize the emerging use and benefits of DPP-4 inhibitors in the treatments of patients with type 2 diabetes. Chen et al. however, claim that the manuscript contains a number of statements which are either inaccurate or require further clarification. Gerich presents two previous studies with fundamentally different methodologies and concludes, 'in a study that compared saxagliptin with glyburide treatment, no statistically significant difference in the incidence of reported and confirmed hypoglycemic events between the two treatments was found'. Chen et al. believe that this conclusion is inaccurate and inappropriate given that the cited saxagliptin study was not a comparative study vs. glyburide but rather assessed the use of saxagliptin in combination with glyburide, thus all subjects in the study would be exposed to the hypoglycemic effects of glyburide.
IT 361442-04-8, Saxagliptin

RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(use and benefits of DPP-4 inhibitors in the treatment of patients with type 2 diabetes)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.

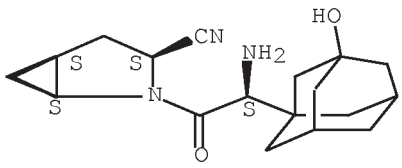


REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 13 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2011:756534 HCAPLUS Full-text
DOCUMENT NUMBER: 156:185905
TITLE: QbD, control strategy and the regulatory experience
AUTHOR(S): Didonato, Gerald C.; Liebowitz, Stephen M.
CORPORATE SOURCE: Bristol-Myers Squibb Company, Princeton, NJ, 08534, USA
SOURCE: Chimica Oggi (2011), 29(2), 34-37
CODEN: CHOGDS; ISSN: 0392-839X
PUBLISHER: Tekno Scienze
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 17 Jun 2011
AB A review. Quality by Design (QbD) is a science and risk-based approach to pharmaceutical development. Products developed under a QbD paradigm create a knowledge base to formulate a holistic control strategy that assures conformance of a drug product to its intended performance profile. Saxagliptin, a new drug for the treatment of Type II diabetes, was developed under QbD principles and submitted for regulatory approval in the US, EU and several other countries. Development experimentation to support the control strategy and its presentation in the applications are discussed.
IT 361442-04-8, Saxagliptin
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(drug developed under quality by design may be useful to formulate holistic control strategy to assure product with its intended performance profile like saxagliptin that presented to regulatory approval for treatment of type II diabetes)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile,

2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 14 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2011:748467 HCAPLUS Full-text
DOCUMENT NUMBER: 156:167858
TITLE: Clinical Pharmacology of Incretin Therapies for Type 2 Diabetes Mellitus: Implications for Treatment
AUTHOR(S): Neumiller, Joshua J.
CORPORATE SOURCE: College of Pharmacy, Washington State University, Spokane, WA, USA
SOURCE: Clinical Therapeutics (2011), 33(5), 528-576
CODEN: CLTHDG; ISSN: 0149-2918
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 16 Jun 2011
AB A review. Background: Increased understanding of the role of incretin hormones in maintaining glucose homeostasis has enabled the development of pharmacotherapies that target deficient incretin activity in type 2 diabetes mellitus (T2DM). Incretin therapies are premised on 1 of 2 approaches: (1) augmenting the activity of the hormone glucagon-like peptide (GLP)-1 (GLP-1 receptor agonists) and (2) inhibiting the degradation of GLP-1 by dipeptidyl peptidase (DPP)-4 (DPP-4 inhibitors). Objective: This review discusses the pharmacokinetic properties and clin. profiles of the GLP-1 receptor agonists (exenatide twice daily, liraglutide once daily, exenatide once weekly, taspoglutide, and albiglutide) and the DPP-4 inhibitors (sitagliptin, saxagliptin, vildagliptin, and alogliptin) available for use or in late-stage development. Methods: A search of PubMed for literature published between 2000 and mid-2010 was conducted using the names of each agent as key words. Phase III and IV studies were included in the review of efficacy and tolerability. Supplemental searches of abstrs. from major diabetes conferences provided addnl. information on pharmacokinetic properties. Searches of all reference lists were performed to identify addnl. refs. of interest. Results: The PubMed search identified multiple randomized, controlled clin. studies of the GLP-1 receptor agonists and the DPP-4 inhibitors administered as monotherapy or in combination regimens. Redns. from baseline in glycosylated Hb ranged from 0.4% to 1.5% with exenatide 5 to 10 μg/d (7 studies), 0.6% to 1.5% with liraglutide 0.6 to 1.8

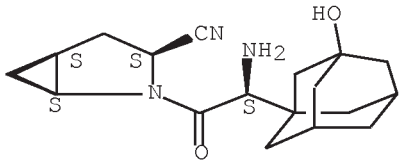
mg/d (6 studies), 0.3% to 1.0% with sitagliptin 25 to 200 mg/d (9 studies), 0.5% to 0.9% with saxagliptin 2.5 to 10 mg/d (3 studies), 0.4% to 1.0% with vildagliptin 50 to 100 mg/d (6 studies), and 0.4% to 0.8% with alogliptin 12.5 to 25 mg/d (4 studies). Dosage adjustments and caution in prescribing incretin therapies are recommended in patients with renal disease, with those recommendations varying based on the agent and the degree of dysfunction. Incretin therapies have been associated with few interactions with commonly used antihyperglycemic and cardiovascular therapies. Conclusion: Based on the pharmacokinetic and therapeutic characteristics described in previously published Phase III and IV studies of incretin therapies, these agents may provide an option for the management of T2DM.

IT 361442-04-8, Saxagliptin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(glucagon-like peptide-1 receptor agonist and DPP-4 inhibitors sitagliptin, saxagliptin, vildagliptin and alogliptin administered as monotherapy or in combination regimens may be helpful in treatment of patient with type 2 diabetes mellitus)

RN 361442-04-8 HCAPLUS

CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)

REFERENCE COUNT: 167 THERE ARE 167 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 15 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN

ACCESSION NUMBER: 2011:736727 HCAPLUS Full-text

DOCUMENT NUMBER: 156:113716

TITLE: DPP-4 inhibitors: impact on glycemic control and cardiovascular risk factors

AUTHOR(S): Dicker, Dror

CORPORATE SOURCE: Internal Medicine D and Obesity Clinic, Hasharon Hospital, Rabin Medical Center, Tel Aviv University, Tel Aviv-Jaffa, Israel

SOURCE: Diabetes Care (2011), 34(Suppl. 2), S276-S278
CODEN: DICAD2; ISSN: 0149-5992

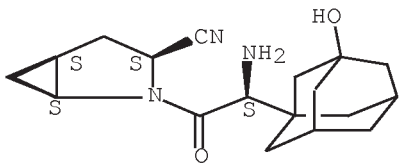
PUBLISHER: American Diabetes Association, Inc.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

ED Entered STN: 14 Jun 2011
AB A review on the dipeptidyl peptidase 4 inhibitors namely, sitagliptin, saxagliptin, and vildagliptin as treatment for diabetes.
IT 361442-04-8, Saxagliptin
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(impact of DPP-4 inhibitors on glycemic control and cardiovascular risk factors)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 16 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2011:556777 HCAPLUS Full-text
DOCUMENT NUMBER: 156:46211
TITLE: Potential effects of DPP-4 inhibitors on cardiovascular disease
AUTHOR(S): Fonseca, Vivian A.
CORPORATE SOURCE: Italy
SOURCE: Hot Topics in Cardiometabolic Disorders (2010), (2), 17-21
CODEN: HTCDBS; ISSN: 2037-9080
URL: http://www.hottopicsin.com/dwl/potential effects of dpp-4_inhibitors_on_cardiovascular_disease_13501cdf35b854e3632b.pdf

PUBLISHER: FBCommunication srl.
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English
ED Entered STN: 05 May 2011
AB A review. Dipeptidyl peptidase 4 inhibitors (DPP-4 inhibitors) are a relatively new class of drugs used for the treatment of diabetes. They exert their effect by inhibiting the breakdown of endogenous glucagon-like peptides (GLP-1 and 2) and glucose-dependent insulinotropic peptide (GIP), resulting in an increase in glucose mediated insulin secretion and a suppression of glucagon secretion. Three DPP-4 inhibitors are currently on

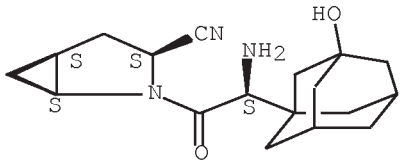
the market: sitagliptin, saxagliptin and vildagliptin. Of these, only sitagliptin and saxagliptin are currently available in the United States, whereas all three are available in Europe. Several other DPP-4 inhibitors are currently in the development stage. Because of the known increased incidence of cardiovascular disease in diabetes, regulatory authorities such as the Food and Drug Administration (FDA) are requiring long-term cardiovascular safety in the development of new diabetes medications while maintaining the current efficacy guidelines with regard to glucose control. Since GLP-1 is known to have many effects beyond glucose lowering, including cardiovascular protective effects, there is interest in determining whether DPP-4 inhibitors will also have similar effects. DPP-4 inhibitors have been shown to improve glucose control without weight gain, hypoglycemia or an increase in blood pressure, and some have even exhibited a significant decrease in the risk of major cardiovascular events. They are consequently considered to be a promising drug class that may meet the demands for both efficacy in the treatment of diabetes, as well as a safe cardiovascular profile. Although many short-term studies have been encouraging, long-term clin. trials are needed to determine whether DPP-4 inhibitors are clearly safe in terms of cardiovascular risk, and whether they may even exert a potential cardiovascular benefit.

IT 361442-04-8, Saxagliptin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(dipeptidyl peptidase-4 inhibitor saxagliptin may be useful to improve glucose control without weight gain, hypoglycemia and to reduce risk of cardiovascular event in diabetes patient with cardiovascular disease)

RN 361442-04-8 HCAPLUS

CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.

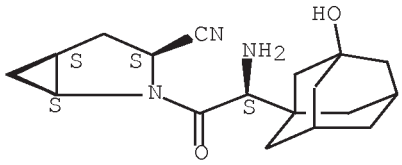


REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 17 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2011:438689 HCAPLUS Full-text
DOCUMENT NUMBER: 155:291988
TITLE: Glucagon-like peptide-1-based therapies and cardiovascular disease: looking beyond glycemic control
AUTHOR(S): Anagnostis, P.; Athyros, V. G.; Adamidou, F.; Panagiotou, A.; Kita, M.; Karagiannis, A.;

Mikhailidis, D. P.
CORPORATE SOURCE: Endocrinology Clinic, Hippokration Hospital, Thessaloniki, Greece
SOURCE: Diabetes, Obesity and Metabolism (2011), 13(4), 302-312
CODEN: DOMEF6; ISSN: 1462-8902
PUBLISHER: Wiley-Blackwell
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 08 Apr 2011
AB A review. Type 2 diabetes mellitus is a well-established risk factor for cardiovascular disease (CVD). New therapeutic approaches have been developed recently based on the incretin phenomenon, such as the degradation-resistant incretin mimetic exenatide and the glucagon-like peptide-1 (GLP-1) analog liraglutide, as well as the dipeptidyl dipeptidase (DPP)-4 inhibitors, such as sitagliptin, vildagliptin, saxagliptin, which increase the circulating bioactive GLP-1. GLP-1 exerts its glucose-regulatory action via stimulation of insulin secretion and glucagon suppression by a glucose-dependent way, as well as by weight loss via inhibition of gastric emptying and reduction of appetite and food intake. These actions are mediated through GLP-1 receptors (GLP-1Rs), although GLP-1R-independent pathways have been reported. Except for the pancreatic islets, GLP-1Rs are also present in several other tissues including central and peripheral nervous systems, gastrointestinal tract, heart and vasculature, suggesting a pleiotropic activity of GLP-1. Indeed, accumulating data from both animal and human studies suggest a beneficial effect of GLP-1 and its metabolites on myocardium, endothelium and vasculature, as well as potential anti-inflammatory and antiatherogenic actions. Growing lines of evidence have also confirmed these actions for exenatide and to a lesser extent for liraglutide and DPP-4 inhibitors compared with placebo or standard diabetes therapies. This suggests a potential cardioprotective effect beyond glucose control and weight loss. Whether these agents actually decrease CVD outcomes remains to be confirmed by large randomized placebo-controlled trials. This review discusses the role of GLP-1 on the cardiovascular system and addresses the impact of GLP-1-based therapies on CVD outcomes.
IT 361442-04-8, Saxagliptin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(dipeptidyl dipeptidase-4 inhibitor such as saxagliptin increased circulating bioactive GLP-1 which exerted its glucose-regulatory action via stimulation of insulin secretion and glucagon suppression in patient with type 2 diabetes mellitus)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.

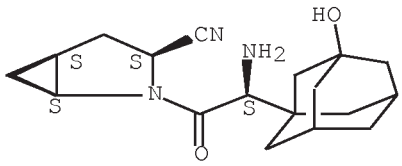


OS.CITING REF COUNT: 7 THERE ARE 7 CAPLUS RECORDS THAT CITE THIS RECORD (8 CITINGS)
REFERENCE COUNT: 125 THERE ARE 125 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 18 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2011:350190 HCAPLUS Full-text
DOCUMENT NUMBER: 155:647621
TITLE: New drug therapy for Type 2 diabetes mellitus: DPP-IV inhibitors
AUTHOR(S): Kulkarni, Vivek S.; Senthil Kumar, G. P.; Lele, Manish D.; Gaikwad, Dinanath T.; Patil, Manoj D.; Gavitre, Bhaskar B.; Bobe, Kisan R.
CORPORATE SOURCE: Indira Institute of Pharmacy, Devrukh, 415804, India
SOURCE: International Journal of Pharmaceutical Sciences Review and Research (2011), 6(2), 147-151
CODEN: IJPSRR; ISSN: 0976-044X
URL: http://globalresearchonline.net/journalcontents/volume6issue2/Article-027.pdf

PUBLISHER: Global Research Online
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English
ED Entered STN: 22 Mar 2011
AB A review. Drugs inhibiting the enzyme Dipeptidyl peptidase-IV are under development in preclin. and clin. studies. These drugs have potential to treat the Type 2 diabetes mellitus. DPP-IV enzyme inhibits rapidly the incretin hormones Glucagon like peptide-1 which is released after food administration to increase insulin level. DPP-IV inhibitor drugs are orally bioactive and after administration stabilize endogenous GLp-1 level and induce insulin secretion in glucose dependent manner. Drug sitagliptin is approved by US FDA. And other drugs like vidagliptin, saxagliptin are under development and late stages of clin. trials. So, DPP-IV inhibitors drugs are good choice for treatment of T2DM with very less side effects.
IT 361442-04-8, Saxagliptin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(dipeptidyl peptidase-IV inhibitors as a new drug therapy for type 2 diabetes mellitus)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

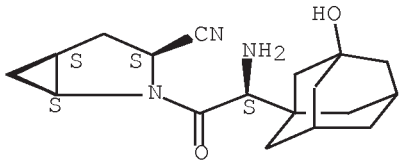
Absolute stereochemistry.



REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 19 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2011:218071 HCAPLUS Full-text
DOCUMENT NUMBER: 155:398027
TITLE: Dipeptidyl peptidase-4 inhibitors in the management of type 2 diabetes: safety, tolerability, and efficacy
AUTHOR(S): Cox, Mary Elizabeth; Rowell, Jennifer; Corsino, Leonor; Green, Jennifer B.
CORPORATE SOURCE: Department of Medicine, Division of Endocrinology, Metabolism, and Nutrition, Duke University Medical Center, Durham, NC, USA
SOURCE: Drug, Healthcare and Patient Safety (2010), 2, 7-19
CODEN: DHPSBA; ISSN: 1179-1365
URL: http://www.dovepress.com/getfile.php?fileID=5719
PUBLISHER: Dove Medical Press Ltd.
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English
ED Entered STN: 22 Feb 2011
AB A review. Although glycemic control is an important and effective way to prevent and minimize the worsening of diabetes-related complications, type 2 diabetes is a progressive disease which often proves difficult to manage. Most affected patients will eventually require therapy with multiple medications in order to reach appropriate glycemic targets. The dipeptidyl peptidase-4 (DPP-4) inhibitors constitute a relatively new class of oral medications for the treatment of type 2 diabetes, which has become widely incorporated into clin. practice. This review summarizes the available data on the efficacy, safety, and tolerability of these medications.
IT 361442-04-8, Saxagliptin
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(safety, tolerability, and efficacy of dipeptidyl peptidase-4 inhibitors in management of type 2 diabetes)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
REFERENCE COUNT: 109 THERE ARE 109 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

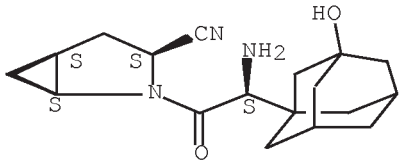
L49 ANSWER 20 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2011:145057 HCAPLUS Full-text
DOCUMENT NUMBER: 155:397940
TITLE: Saxagliptin: a selective DPP-4 inhibitor for the treatment of type 2 diabetes mellitus
AUTHOR(S): Shubrook, Jay; Colucci, Randall; Guo, Aili; Schwartz, Frank
CORPORATE SOURCE: Department of Family Medicine, Ohio University College of Osteopathic Medicine (OU-COM), Athens, OH, 45701, USA
SOURCE: Clinical Medicine Insights: Endocrinology and Diabetes (2011), 4, 1-12
CODEN: CMIEBP; ISSN: 1179-5514
URL:
http://www.la-press.com/redirect_file.php?fileId=3311&filename=2433-

CMED-Saxagliptin:-A-Selective-DPP-4-Inhibitor-for-the-Treatment-of-Type-2-D.pdf&fileType=pdf

PUBLISHER: Libertas Academica
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English
ED Entered STN: 04 Feb 2011
AB A review. The prevalence of type 2 diabetes mellitus is high and growing rapidly. Suboptimal glycemic control provides opportunities for new treatment options to improve the morbidity and mortality of this progressive disease. Saxagliptin, a selective DPP-4 inhibitor, increases endogenous incretin levels and incretin activity. In controlled clin. trials saxagliptin reduces both fasting and postprandial glucose and works in monotherapy and in combination with metformin, TZDs and sulfonylureas. Saxagliptin has a very favorable side effect profile and may have other beneficial non-glycemic effects. The authors review the current available evidence for the safety, efficacy and saxagliptin's place in therapy for type 2 diabetes mellitus. As understanding of the incretin hormones (GLP-1, GIP) expand we may see addnl. important non-glycemic effects that may affect the chronic management of type 2 diabetes mellitus.
IT 361442-04-8, Saxagliptin

RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(saxagliptin as a selective DPP-4 inhibitor for the treatment of type 2 diabetes mellitus)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

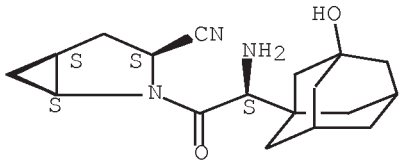
Absolute stereochemistry.



REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 21 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2011:136698 HCAPLUS Full-text
DOCUMENT NUMBER: 154:350909
TITLE: Synthetic approaches to the 2009 new drugs
AUTHOR(S): Liu, Kevin K.-C.; Sakya, Subas M.; O'Donnell, Christopher J.; Flick, Andrew C.; Li, Jin
CORPORATE SOURCE: Pfizer Inc., La Jolla, CA, 92037, USA
SOURCE: Bioorganic & Medicinal Chemistry (2011), 19(3), 1136-1154
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 02 Feb 2011
AB A review. New drugs are introduced to the market every year and each individual drug represents a privileged structure for its biol. target. These new chemical entities (NCEs) provide insights into mol. recognition and also serve as leads for designing future new drugs. This review covers the syntheses of 21 NCEs marketed in 2009.
IT 361442-04-8P, Onglyza
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(synthetic approaches to the 2009 new drugs)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

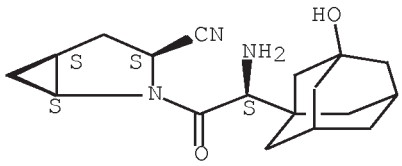
Absolute stereochemistry.



OS.CITING REF COUNT: 5 THERE ARE 5 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)
REFERENCE COUNT: 111 THERE ARE 111 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 22 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2011:57251 HCAPLUS Full-text
DOCUMENT NUMBER: 155:290017
TITLE: Dipeptidyl peptidase-4 inhibitors in the treatment of type 2 diabetes: a comparative review
AUTHOR(S): Deacon, C. F.
CORPORATE SOURCE: Department of Biomedical Sciences, Panum Institute, University of Copenhagen, Copenhagen N, Den.
SOURCE: Diabetes, Obesity and Metabolism (2011), 13(1), 7-18
CODEN: DOMEF6; ISSN: 1462-8902
PUBLISHER: Wiley-Blackwell
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 17 Jan 2011
AB A review. The dipeptidyl peptidase (DPP)-4 inhibitors are a new class of antihyperglycemic agents which were developed for the treatment of type 2 diabetes by rational drug design, based on an understanding of the underlying mechanism of action and knowledge of the structure of the target enzyme. Although they differ in terms of their chemical, they are all small mols. which are orally available. There are some differences between them in terms of their absorption, distribution, metabolism and elimination, as well as in their potency and duration of action, but their efficacy, both in terms of inhibiting plasma DPP-4 activity and as antidiabetic agents, appears to be similar. They improve glycemic control, reducing both fasting and postprandial glucose levels to lower HbA1c levels, without weight gain and with an apparently benign adverse event profile. At present, there seems to be little to distinguish between the different inhibitors in terms of their efficacy as antidiabetic agents and their safety. Long-term accumulated clin. experience will reveal whether compound-related characteristics lead to any clin. relevant differences.
IT 361442-04-8, Saxagliptin
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(dipeptidyl peptidase-4 inhibitors in the treatment of type 2 diabetes)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 19 THERE ARE 19 CAPLUS RECORDS THAT CITE THIS RECORD (20 CITINGS)
REFERENCE COUNT: 84 THERE ARE 84 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 23 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2010:1631727 HCAPLUS Full-text
DOCUMENT NUMBER: 154:124214
TITLE: The role for saxagliptin within the management of type 2 Diabetes mellitus: an update from the 2010 European Association for the Study of Diabetes (EASD) 46th annual meeting and the American Diabetes Association (ADA) 70th scientific session
AUTHOR(S): Aschner, Pablo J.
CORPORATE SOURCE: Javeriana University, Bogota, Colombia
SOURCE: Diabetology & Metabolic Syndrome (2010), 2, 69
CODEN: DMSIBU; ISSN: 1758-5996
URL: http://www.dmsjournal.com/content/pdf/1758-5996-2-69.pdf

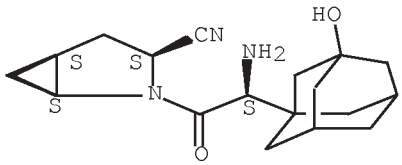
PUBLISHER: BioMed Central Ltd.
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English
ED Entered STN: 31 Dec 2010
AB A review. Saxagliptin is a potent, selective DPP4 inhibitor. Highlights from abstrs. presented at the 2010 meetings of the European Association for the Study of Diabetes and the American Diabetes Association include studies and analyses that shed light on the promising role for saxagliptin within the management of type 2 diabetes mellitus. Data show that saxagliptin combination therapy improves HbA1c levels compared with placebo, particularly in patients with high HbA1c at baseline, long duration of disease, low baseline creatinine clearance, and low homeostasis model assessment 2 β-cell function at baseline. These efficacy benefits are achieved without any increase in hypoglycemia or other adverse events. The study results also show that the saxagliptin plus metformin combination is a good candidate for initial therapy in drug-naive patients treated for as long as 72 wk. Survey data presented confirm that hypoglycemia (and fear of hypoglycemia) is a barrier to patients' acceptance of diabetes treatment, limiting its efficacy. Therefore, therapies such as saxagliptin that have a low risk of hypoglycemia may be more acceptable to patients in helping them to achieve glycemic control and to optimize their quality of life. In

patients with renal impairment, for whom metformin is contraindicated, saxagliptin monotherapy is a promising option for antidiabetic management as, when given at a reduced dose, it is well-tolerated with a safety profile similar to that of placebo.

IT 361442-04-8, Saxagliptin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(saxagliptin was safe and effective in patient with type 2 diabetes mellitus)

RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)
REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 24 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2010:1447898 HCAPLUS Full-text
DOCUMENT NUMBER: 155:200105
TITLE: Clinical overview of saxagliptin for Type 2 diabetes management
AUTHOR(S): Rosenstock, Julio
CORPORATE SOURCE: Dallas Diabetes and Endocrine Center, Dallas, TX, 75230, USA
SOURCE: Expert Review of Endocrinology & Metabolism (2010), 5(6), 809-823
CODEN: EREMBI; ISSN: 1744-6651
PUBLISHER: Expert Reviews Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 22 Nov 2010
AB A review. Saxagliptin (Onglyza, Bristol-Myers Squibb, NJ, USA and AstraZeneca, DE, USA) is a potent, orally active, once-daily dipeptidyl peptidase-4 inhibitor that is indicated as an adjunct to diet and exercise alone, or in combination with metformin, a thiazolidinedione or a sulfonylurea to improve glycemic control in adults with Type 2 diabetes mellitus. By inhibiting dipeptidyl peptidase-4, saxagliptin increases concns. of the intact forms of the incretin hormones, glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide, prolonging their effects.

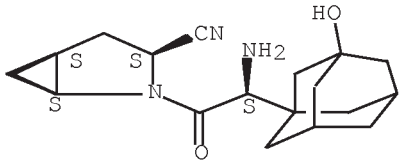
Saxagliptin also improves β-cell function, increases postprandial insulin secretion and reduces postprandial glucagon secretion. Saxagliptin is generally well tolerated with weight-neutral effects and a low incidence of hypoglycemia. Multicenter randomized trials have shown that saxagliptin as monotherapy, as initial therapy with metformin or as add-on therapy with metformin, a sulfonylurea or a thiazolidinedione leads to significant decreases in glycated Hb levels, fasting and postprandial plasma glucose levels and higher percentages of patients attaining target glycated Hb of less than 7% compared with controls.

IT 361442-04-8, Saxagliptin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(clin. overview of saxagliptin for type 2 diabetes management)

RN 361442-04-8 HCAPLUS

CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)

REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 25 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN

ACCESSION NUMBER: 2010:1440105 HCAPLUS Full-text

DOCUMENT NUMBER: 153:595329

TITLE: Saxagliptin (Onglyza): new inhibitor of the dipeptidylpeptidase-4 for the oral treatment of type 2 diabetes

AUTHOR(S): Scheen, A. J.

CORPORATE SOURCE: Service de Diabetologie, Nutrition et Maladies metaboliques et Unite de Pharmacologie clinique, CHU Liege, Universite de Liege, Belg.

SOURCE: Revue Medicale de Liege (2010), 65(9), 527-532
CODEN: RMLIAC; ISSN: 0370-629X

PUBLISHER: Revue Medicale de Liege

DOCUMENT TYPE: Journal; General Review

LANGUAGE: French

ED Entered STN: 21 Nov 2010

AB A review. Saxagliptin (Onglyza) is a specific and reversible inhibitor of dipeptidylpeptidase-4 (DPP-4), which inhibits the activity of the enzyme for at least 24 h after one single oral administration. It increases the

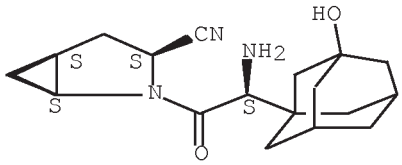
circulating levels of incretin hormones (GLP-1, GIP), which contributes to amplify the insulin secretory response to meals and to reduce postprandial hyperglycemia and, subsequently, fasting glycemia. Saxagliptin, 5 mg once daily, has been shown to be effective in patients with type 2 diabetes treated with diet alone, metformin, sulfonylurea or glitazone, with a favorable tolerance profile. Reduction in glycated Hb (HbA1c) averaged 0.6-0.8 %, without increasing the risk of hypoglycemia or promoting weight gain. The only indication of saxagliptin that is currently reimbursed in Belgium is the treatment of patients not controlled with metformin, the oral antidiabetic agent that is recommended as first line therapy in the management of type 2 diabetes.

IT 361442-04-8, Saxagliptin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Onglyza; Saxagliptin as new DPP-4 inhibitor for oral treatment of type 2 diabetes)

RN 361442-04-8 HCAPLUS

CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)

REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 26 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN

ACCESSION NUMBER: 2010:1361201 HCAPLUS Full-text

DOCUMENT NUMBER: 155:173558

TITLE: Saxagliptin: a review

AUTHOR(S): Evans, Marc

CORPORATE SOURCE: UK

SOURCE: British Journal of Diabetes & Vascular Disease (2010), 10(1), 14-20
CODEN: BJDVAI; ISSN: 1474-6514

PUBLISHER: Sage Publications Ltd.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

ED Entered STN: 02 Nov 2010

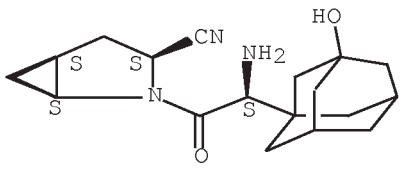
AB A review. Modulation of the effects of incretin hormones provides a novel mechanism of action for some of the newer therapies for patients with type 2 diabetes. The selective, reversible dipeptidyl peptidase-4 inhibitor saxagliptin has demonstrated robust improvements in glycemic control, as

monotherapy or as add-on therapy to metformin, sulfonylureas and thiazolidine-diones, without significant change in body weight and while exhibiting a low risk of hypoglycemia.

IT 361442-04-8, Saxagliptin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(saxagliptin alone or in combination with metformin, sulfonylurea and thiazolidinedione showed improvement in glycemic control and no change in body weight in patient with type 2 diabetes)

RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 27 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2010:1327711 HCAPLUS Full-text
DOCUMENT NUMBER: 155:82260
TITLE: Liraglutide: effects beyond glycemic control in diabetes treatment
AUTHOR(S): McGill, J. B.
CORPORATE SOURCE: Division of Endocrinology, Metabolism and Lipid Research, Washington University in St. Louis, St. Louis, MO, 63110, USA
SOURCE: International Journal of Clinical Practice, Supplement (2010), 64(Suppl. 167), 28-34
CODEN: ICPSFY; ISSN: 1368-504X
URL: http://onlinelibrary.wiley.com/doi/10.1111/j.1742-1241.2010.02495.x/pdf

PUBLISHER: Wiley-Blackwell
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English
ED Entered STN: 26 Oct 2010
AB A review. To review the non-glycemic effects of liraglutide, including potential improvements in body weight, systolic blood pressure (SBP) and pancreatic beta-cell function. Liraglutide induced weight loss of around 2-3 kg compared with weight increases of 1-2 kg with active comparators such as insulin glargine, rosiglitazone and glimepiride. Exenatide demonstrated

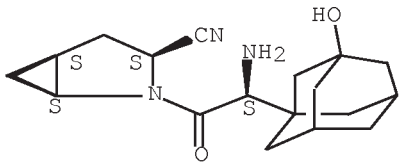
similar weight benefits to liraglutide, but the dipeptidyl peptidase-4 (DPP-4) inhibitors, sitagliptin, saxagliptin and vildagliptin, were weight neutral. Liraglutide was associated with decreases in SBP of 2-7 mmHg, whereas exenatide, vildagliptin and sitagliptin demonstrated SBP redns. of around 2-3 mmHg. Measures of pancreatic beta-cell function were improved with liraglutide vs. placebo, rosiglitazone and exenatide. However, DPP-4 inhibitors appear to have less effect on beta-cell function than glucagon-like peptide-1 (GLP-1) receptor agonists. In addition to glycemic control, liraglutide and the other incretin-based therapies offer addnl. non-glycemic benefits to varying degrees. The ability of GLP-1 receptor agonists to provide modest, but clin. relevant improvements in body weight and SBP, and to potentially benefit beta-cell function make them an exciting therapeutic option for individuals with diabetes. In contrast, DPP-4 inhibitors are weight neutral and may have lesser benefits on beta-cell function.

IT 361442-04-8, Saxagliptin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(saxagliptin did not affect body weight in patient with diabetes)

RN 361442-04-8 HCAPLUS

CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)

REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 28 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN

ACCESSION NUMBER: 2010:1318024 HCAPLUS Full-text

DOCUMENT NUMBER: 155:82235

TITLE: Saxagliptin: a new dipeptidyl peptidase 4 inhibitor for type 2 diabetes

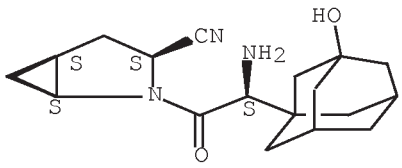
AUTHOR(S): Borja-Hart, Nancy L.; Whalen, Karen L.

CORPORATE SOURCE: Department of Pharmacy Practice, College of Pharmacy, Nova Southeastern University, Ft. Lauderdale, FL, USA

SOURCE: Annals of Pharmacotherapy (2010), 44(6), 1046-1053
CODEN: APHRER; ISSN: 1542-6270
URL: http://www.theannals.com/cgi/content/abstract/44/6/1046

PUBLISHER: Harvey Whitney Books Co.
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English
ED Entered STN: 24 Oct 2010
AB OBJECTIVE: To review the pharmacol., pharmacokinetics, efficacy, and safety of saxagliptin, a new dipeptidyl peptidase-4 (DPP-4) inhibitor for the treatment of type 2 diabetes. DATA SOURCES: Searches of PubMed (1966-March 2010) and International Pharmacy Abstrs. (1970-March 2010) were conducted using the key words saxagliptin, Onglyza, and BMS-477118. A review of bibliogs. of retrieved articles was also performed to identify addnl. refs. STUDY SELECTION AND DATA Extraction: All identified studies published in English and involving efficacy and safety of saxagliptin in the treatment of type 2 diabetes were reviewed. DATA SYNTHESIS: Saxagliptin is a competitive inhibitor of DPP-4 that slows the degradation of incretin hormones, thereby stimulating insulin secretion, reducing postprandial glucagon, and decreasing glucose levels. Saxagliptin is well absorbed after oral administration and demonstrates a pharmacokinetic profile that is compatible with once-daily dosing. Clin. trials with saxagliptin monotherapy for the treatment of type 2 diabetes showed a reduction in Hb A1c (A1C) of 0.43-0.9%. Saxagliptin has demonstrated similar redns. in A1C when used as add-on therapy with metformin, sulfonylureas, and thiazolidinediones. The combination of saxagliptin and metformin for initial therapy in treatment-naive patients was associated with greater improvements in A1C than either agent alone. In general, saxagliptin therapy is well tolerated. The most common adverse effects occurring in clin. trials were headache, nasopharyngitis, upper respiratory tract infections, and urinary tract infections. CONCLUSIONS: Saxagliptin is effective as monotherapy or add-on therapy for the management of type 2 diabetes. Because saxagliptin has a higher cost and reduces A1C and other surrogate markers of glucose control to a lesser extent than other well-validated therapies, such as metformin, saxagliptin should be reserved for patients who fail or are intolerant of conventional treatments for type 2 diabetes.
IT 361442-04-8, Onglyza
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(onglyza alone or in combination with metformin, sulfonylureas and thiazolidinediones showed favorable pharmacokinetic profile and was safe, effective in treatment of patient with type 2 diabetes)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

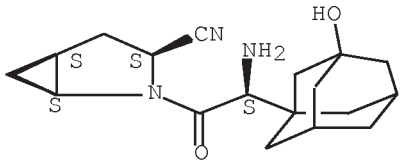
Absolute stereochemistry.



OS.CITING REF COUNT: 6 THERE ARE 6 CAPLUS RECORDS THAT CITE THIS RECORD (6 CITINGS)
REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 29 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2010:1268539 HCAPLUS Full-text
DOCUMENT NUMBER: 155:111600
TITLE: DPP-4 inhibitors: What may be the clinical differentiators?
AUTHOR(S): Gerich, John
CORPORATE SOURCE: Clinical Research Center, University of Rochester School of Medicine, Rochester, NY, 14642, USA
SOURCE: Diabetes Research and Clinical Practice (2010), 90(2), 131-140
CODEN: DRCPE9; ISSN: 0168-8227
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 12 Oct 2010
AB A review. Attenuation of the prandial incretin effect, mediated by glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), contributes to hyperglycemia in type 2 diabetes mellitus (T2DM). Since the launch of sitagliptin in 2006, a compelling body of evidence has accumulated showing that dipeptidyl peptidase-4 (DPP-4) inhibitors, which augment endogenous GLP-1 and GIP levels, represent an important advance in the management of T2DM. Currently, three DPP-4 inhibitors - sitagliptin, vildagliptin and saxagliptin - have been approved in various countries worldwide. Several other DPP-4 inhibitors, including linagliptin and alogliptin, are currently in clin. development. As understanding of, and experience with, the growing number of DPP-4 inhibitors broadens, increasing evidence suggests that the class may offer advantages over other antidiabetic drugs in particular patient populations. The expanding evidence base also suggests that certain differences between DPP-4 inhibitors may prove to be clin. significant. This therapeutic diversity should help clinicians tailor treatment to the individual patient, thereby increasing the proportion that safely attain target HbA1c levels, and reducing morbidity and mortality. This review offers an overview of DPP-4 inhibitors in T2DM and suggests some characteristics that may provide clin. relevant differentiators within this class.
IT 361442-04-8, Saxagliptin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(clin. differentiators of dipeptidyl peptidase 4 inhibitors)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 12 THERE ARE 12 CAPLUS RECORDS THAT CITE THIS RECORD (12 CITINGS)
REFERENCE COUNT: 87 THERE ARE 87 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

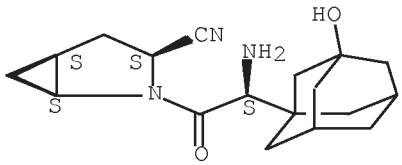
L49 ANSWER 30 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2010:1258350 HCAPLUS Full-text
DOCUMENT NUMBER: 155:58546
TITLE: Saxagliptin: a dipeptidyl peptidase-4 inhibitor for the treatment of type 2 diabetes mellitus
AUTHOR(S): Neumiller, Joshua J.; Campbell, R. Keith
CORPORATE SOURCE: Department of Pharmacotherapy, College of Pharmacy, Washington State University, Spokane, USA
SOURCE: American Journal of Health-System Pharmacy (2010), 67(18), 1515-1525
CODEN: AHSPEK; ISSN: 1079-2082
PUBLISHER: American Society of Health-System Pharmacists
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 08 Oct 2010
AB A review. Purpose. The pharmacol., pharmacokinetics, efficacy, safety, and dosage and administration of saxagliptin are reviewed. Summary. Saxagliptin is a selective, reversible inhibitor of dipeptidyl peptidase-4 (DPP-4) approved for the treatment of type 2 diabetes mellitus in adults. By inhibiting DPP-4, saxagliptin reduces the degradation of endogenous incretin hormones, resulting in increased glucose-dependent insulin release and decreased glucagon secretion from the pancreas. Saxagliptin is rapidly absorbed after oral administration, and its pharmacokinetic profile allows for once-daily oral administration. Clin. trials of saxagliptin as monotherapy and as combination therapy with other oral antidiabetic medications including metformin, glyburide, pioglitazone, and rosiglitazone have demonstrated clin. benefits in various glycemic endpoints, including glycosylated Hb (HbA1c), fasting plasma glucose (FPG), and postprandial glucose (PPG) levels over 24 to 102 wk of therapy. Due to its glucose-dependent mechanism of action, saxagliptin as mono-therapy or in combination with metformin results in a low risk for hypoglycemia in patients with type 2 diabetes. Saxagliptin was generally well tolerated in clin. trials, with headache, upper-respiratory-tract infection, and urinary tract infection being the most common adverse events. Saxagliptin has demonstrated a low risk for drug-drug interactions. For patients with moderate or severe renal impairment or end-stage renal disease or patients taking a strong inhibitor of cytochrome P 450 isoenzyme 3A4 or 3A5, the recommended dosage is 2.5 mg once daily. Conclusion. Saxagliptin, a DPP-4 inhibitor approved for the treatment of type 2 diabetes, demonstrated safety

and efficacy in lowering HbA1c, FPG, and PPG levels as both monotherapy and in combination with other oral antidiabetic medications.

IT 361442-04-8, Saxagliptin
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(saxagliptin either alone or in combination with metformin, glyburide, pioglitazone and rosiglitazone was safe and effective in treatment of adult patient with type 2 diabetes mellitus)

RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 7 THERE ARE 7 CAPLUS RECORDS THAT CITE THIS RECORD (8 CITINGS)
REFERENCE COUNT: 71 THERE ARE 71 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d l49 ibib ed abs hitstr 31-60
YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS' - CONTINUE? (Y)/N:y

L49 ANSWER 31 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2010:1245202 HCAPLUS Full-text
DOCUMENT NUMBER: 154:400831
TITLE: SLCO1B1 polymorphism and oral antidiabetic drugs
AUTHOR(S): Kalliokoski, Annikka; Neuvonen, Pertti J.; Niemi, Mikko
CORPORATE SOURCE: Research Department, Social Insurance Institution, Helsinki, Finland
SOURCE: Basic & Clinical Pharmacology & Toxicology (2010), 107(4), 775-781
CODEN: BCPTBO; ISSN: 1742-7835
PUBLISHER: Wiley-Blackwell
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 06 Oct 2010

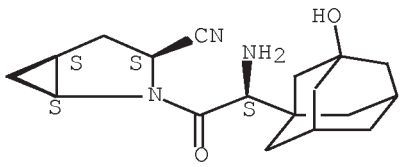
AB A review. Organic anion-transporting polypeptide 1B1 (OATP1B1; gene: SLCO1B1) is an influx transporter expressed on the sinusoidal membrane of human hepatocytes, where it mediates the uptake of its substrates from blood into liver. In vitro, the SLCO1B1 c.521T > C (p.Val174Ala) single-nucleotide polymorphism (SNP) has been associated with reduced and the c.388A > G (p.Asn130Asp) SNP with both enhanced and reduced transport activity of OATP1B1. In vivo in humans, the c.521C allele (present in SLCO1B1*5 and *15 haplotypes) is associated with decreased hepatic uptake and increased plasma concns. of several OATP1B1 substrates. The SLCO1B1*1B (c.388G-c.521T) haplotype is associated with enhanced hepatic uptake and decreased plasma concns. of some OATP1B1 substrates. The SLCO1B1 c.521CC genotype has been associated with an about 60-190% increased, and the SLCO1B*1B/*1B genotype with an about 30% decreased area under the plasma concentration-time curve of repaglinide. Moreover, SLCO1B1 polymorphism can affect the extent of interaction between OATP1B1 inhibitors and repaglinide. Accordingly, SLCO1B1 genotyping may help in choosing the optimal starting dose of repaglinide. In Chinese individuals, the SLCO1B1 c.521C allele has been associated with increased plasma concns. of nateglinide, but the association could not be replicated in Caucasians. SLCO1B1 genotype has had no effect on the pharmacokinetics of rosiglitazone, pioglitazone or their metabolites. The hepatic uptake of metformin is mediated by organic cation transporters 1 and 3, and the liver is not important for the elimination or action of the dipeptidylpeptidase 4 inhibitors sitagliptin, vildagliptin and saxagliptin. Therefore, SLCO1B1 polymorphism unlikely affects the response to these antidiabetics. Possible effects of SLCO1B1 polymorphism on sulfonylureas remain to be investigated.

IT 361442-04-8, Saxagliptin
RL: PKT (Pharmacokinetics); BIOL (Biological study)
(liver was not important for elimination or action of oral saxagliptin in patient with diabetes)

RN 361442-04-8 HCAPLUS

CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 5 THERE ARE 5 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)

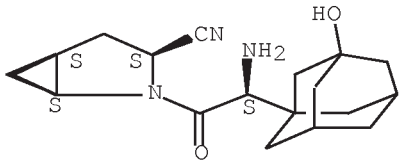
REFERENCE COUNT: 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 32 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN

ACCESSION NUMBER: 2010:1237315 HCAPLUS Full-text

DOCUMENT NUMBER: 153:471412
TITLE: Saxagliptin for type 2 diabetes
AUTHOR(S): Chacra, Antonio R.
CORPORATE SOURCE: Diabetes Center, Federal University of Sao Paulo, Brazil
SOURCE: Diabetes, Metabolic Syndrome and Obesity (2010), 3, 325-335
CODEN: DMSOAD; ISSN: 1178-7007
URL: http://www.dovepress.com/getfile.php?fileID=7746
PUBLISHER: Dove Medical Press Ltd.
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English
ED Entered STN: 05 Oct 2010
AB A review. Saxagliptin (Onglyza) is a potent, selective, once-daily dipeptidyl peptidase-4 (DPP-4) inhibitor indicated for improving glycemic control in patients with type 2 diabetes (T2D). By blocking DPP-4, saxagliptin increases and prolongs the effects of incretins, a group of peptide hormones released by intestinal cells after meals, which stimulate glucose-dependent insulin secretion to lower blood glucose. In controlled clin. trials, saxagliptin administered as monotherapy or in combination with metformin, glyburide, or a thiazolidinedione improved glycemic control in a clin. significant manner, reflected by significant decreases in glycated Hb (monotherapy, -0.5%; add-on to metformin, thiazolidinedione, or sulfonylurea, -0.6% to 0.9%; initial combination with metformin, -2.5%), fasting plasma glucose, and postprandial glucose compared with controls. Addnl., saxagliptin improved β-cell function, reflected as increases in homeostasis model assessment (HOMA)-2β. Saxagliptin was generally well tolerated; it did not increase hypoglycemia compared with controls, and was weight neutral. A meta-anal. of Phase II and III trials showed that saxagliptin did not increase the risk of major cardiovascular events. Professional organizations have updated their guidelines for T2D to include a DPP-4 inhibitor as an early treatment option - either as initial therapy in combination with metformin, or as add-on therapy for patients whose glycemia is inadequately controlled by a single oral antidiabetic drug.
IT 361442-04-8, Onglyza
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Onglyza inhibited dipeptidyl peptidase-4 with increased, prolonged effect of incretin secreted by intestinal cell that stimulated glucose-dependent insulin secretion which decreased blood glucose in patient with type 2 diabetes)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 33 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2010:1209603 HCAPLUS Full-text
DOCUMENT NUMBER: 155:260
TITLE: Dipeptidylpeptitase-4 inhibitors (gliptins)
AUTHOR(S): Scheen, Andre J.
CORPORATE SOURCE: Division of Clinical Pharmaccology and Division of Diabetes, Nutrition and Metabolic Disorders, Department of Medicine, CHU Sart Tilman, University of Liege, Liege, Belg.
SOURCE: Clinical Pharmacokinetics (2010), 49(9), 573-588
CODEN: CPKNDH; ISSN: 0312-5963
PUBLISHER: Wolters Kluwer Health
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 28 Sep 2010
AB A review. Patients with type 2 diabetes mellitus (T2DM) are generally treated with many pharmacol. compds. and are exposed to a high risk of drug-drug interactions. Indeed, blood glucose control usually requires a combination of various glucose-lowering agents, and the recommended global approach to reduce overall cardiovascular risk generally implies administration of several protective compds., including HMG-CoA reductase inhibitors (statins), antihypertensive compds. and antiplatelet agents. New compds. have been developed to improve glucose-induced β-cell secretion and glucose control, without inducing hypoglycemia or weight gain, in patients with T2DM. Dipeptidylpeptidase-4 (DPP-4) inhibitors are novel oral glucose-lowering agents, which may be used as monotherapy or in combination with other antidiabetic compds., metformin, thiazolidinediones or even sulfonylureas. Sitagliptin, vildagliptin and saxagliptin are already on the market, either as single agents or in fixed-dose combined formulations with metformin. Other compds., such as alogliptin and linagliptin, are in a late phase of development. This review summarizes the available data on drug-drug interactions reported in the literature for these five DDP-4 inhibitors: sitagliptin, vildagliptin, saxagliptin, alogliptin and linagliptin. Possible pharmacokinetic interferences have been investigated between each of these compds. and various pharmacol. agents, which were selected because there are other glucose-lowering agents (metformin, glibenclamide [glyburide], pioglitazone/rosiglitazone) that may be prescribed in combination with DPP-4 inhibitors, other drugs that are currently used in patients with T2DM (statins, antihypertensive agents),

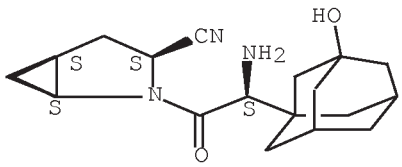
compds. that are known to interfere with the cytochrome P 450 (CYP) system (ketoconazole, diltiazem, rifampicin [rifampin]) or with P-glycoprotein transport (ciclosporin), or agents with a narrow therapeutic safety window (warfarin, digoxin). Generally speaking, almost no drug-drug interactions or only minor drug-drug interactions have been reported between DPP-4 inhibitors and any of these drugs. The gliptins do not significantly modify the pharmacokinetic profile and exposure of the other tested drugs, and the other drugs do not significantly alter the pharmacokinetic profile of the gliptins or exposure to these. The only exception concerns saxagliptin, which is metabolized to an active metabolite by CYP3A4/5. Therefore, exposure to saxagliptin and its primary metabolite may be significantly modified when saxagliptin is coadministered with specific strong inhibitors (ketoconazole, diltiazem) or inducers (rifampicin) of CYP3A4/5 isoforms. The absence of significant drug-drug interactions could be explained by the favorable pharmacokinetic characteristics of DPP-4 inhibitors, which are not inducers or inhibitors of CYP isoforms and are not bound to plasma proteins to a great extent. Therefore, according to these pharmacokinetic findings, which were generally obtained in healthy young male subjects, no dosage adjustment is recommended when gliptins are combined with other pharmacol. agents in patients with T2DM, with the exception of a reduction in the daily dosage of saxagliptin when this drug is used in association with a strong inhibitor of CYP3A4/A5. It is worth noting, however, that a reduction in the dose of sulfonylureas is usually recommended when a DPP-4 inhibitor is added, because of a pharmacodynamic interaction (rather than a pharmacokinetic interaction) between the sulfonylurea and the DPP-4 inhibitor, which may result in a higher risk of hypoglycemia. Otherwise, any gliptin may be combined with metformin or a thiazolidinedione (pioglitazone, rosiglitazone), leading to a significant improvement in glycemic control without an increased risk of hypoglycemia or any other adverse event in patients with T2DM. Finally, the absence of drug-drug interactions in clin. trials in healthy subjects requires further evidence from large-scale studies, including typical subjects with T2DM - in particular, multimorbid and geriatric patients receiving polypharmacy.

IT 361442-04-8, Saxagliptin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(saxagliptin showed minor drug-drug interaction with statins, cyclosporine, antihypertensive agent and glucose-lowering agents but did not modify their pharmacokinetic profile in patient with type 2 diabetes mellitus)

RN 361442-04-8 HCAPLUS

CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

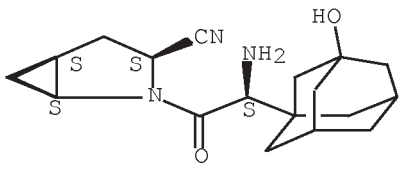
Absolute stereochemistry.



OS.CITING REF COUNT: 25 THERE ARE 25 CAPLUS RECORDS THAT CITE THIS RECORD (26 CITINGS)
REFERENCE COUNT: 100 THERE ARE 100 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 34 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2010:1208417 HCAPLUS Full-text
DOCUMENT NUMBER: 153:397494
TITLE: Saxagliptin, a dipeptidyl peptidase IV inhibitor for the treatment of type 2 diabetes. [Erratum to document cited in CA151:023607]
AUTHOR(S): Gallwitz, Baptist
CORPORATE SOURCE: Department of Medicine IV, Eberhard-Karls-University, Tuebingen, 72076, Germany
SOURCE: IDrugs (2009), 12(5), 200
CODEN: IDRUFN; ISSN: 2040-3410
PUBLISHER: BioMed Central Ltd.
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English
ED Entered STN: 28 Sep 2010
AB A review. On page 909, in the left column, in paragraph 4, in lines 6 and 8, "higher" and "lower", were incorrectly given, and should read: "lower" and "higher", resp.; and in line 9, "healthy volunteers than patients.", was incorrectly given, and should read: "healthy volunteers than in patients.".
IT 361442-04-8, Saxagliptin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(dipeptidyl peptidase IV inhibitor saxagliptin was safe and effective in improving glucose tolerance and increasing insulin level in animal and patient with type 2 diabetes mellitus (Erratum))
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

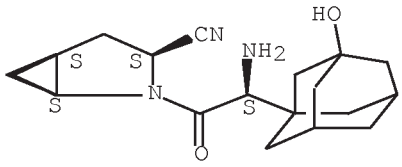
Absolute stereochemistry.



L49 ANSWER 35 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2010:1105677 HCAPLUS Full-text

DOCUMENT NUMBER: 154:556461
TITLE: Saxagliptin: a new dipeptidyl peptidase-IV inhibitor for the treatment of type 2 diabetes
AUTHOR(S): Tan, Ling; Xia, Lu-feng; Sun, Chun-hua
CORPORATE SOURCE: Department of Pharmacy, Beijing Hospital, The Ministry of Health, Beijing, 100730, Peop. Rep. China
SOURCE: Zhongguo Xinyao Zazhi (2010), 19(13), 1099-1102
CODEN: ZXZHA6; ISSN: 1003-3734
PUBLISHER: Zhongguo Xinyao Zazhi Youxian Gongsi
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Chinese
ED Entered STN: 05 Sep 2010
AB A review. Saxagliptin, a potent and selective reversible inhibitor of dipeptidyl peptidase-IV, has been approved for the treatment of type 2 diabetes in adults. Saxagliptin reduces the degradation of the incretin hormone glucagon-like peptide-1, thereby enhancing its actions, and is associated with improved beta-cell function and suppression of glucagon secretion. Clin. trials have shown that saxagliptin improves glycemic control in monotherapy and provides addnl. efficacy when used in combination with other oral antidiabetic agents (metformin, sulfonylurea and thiazolidinedione). There is a low risk of hypoglycemia. Saxagliptin is reported to be well tolerated with adverse drug reactions profile similar to placebo.
IT 361442-04-8, Saxagliptin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(saxagliptin: dipeptidyl peptidase-IV inhibitor for treatment of type 2 diabetes)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

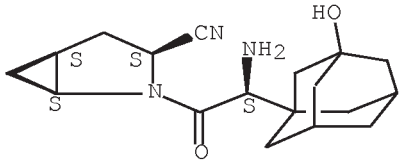
Absolute stereochemistry.



L49 ANSWER 36 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2010:1098157 HCAPLUS Full-text
DOCUMENT NUMBER: 154:50343
TITLE: New drug saxagliptin for treating type 2 diabetes mellitus
AUTHOR(S): Liu, Ping; Zhou, Jing; Yang, Xiaojun; Li, Jin; Cheng, Liyu
CORPORATE SOURCE: Journal of China Pharmacy, Chongqing, 400042, Peop.

Rep. China
SOURCE: Zhongguo Yaofang (2010), 21(1), 80-82
CODEN: ZYHAA4; ISSN: 1001-0408
PUBLISHER: Zhongguo Yaofang Zazhishe
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Chinese
ED Entered STN: 02 Sep 2010
AB A review with 11 refs., is given on new drug saxagliptin for treating type 2 diabetes mellitus. Saxagliptin is a new antidiabetic drug for treating type 2 diabetes mellitus, which has been approved by FDA.
IT 361442-04-8, Saxagliptin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(new drug saxagliptin for treating type 2 diabetes mellitus)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile,
2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-,
(1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



L49 ANSWER 37 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2010:1075988 HCAPLUS Full-text
DOCUMENT NUMBER: 154:502905
TITLE: Pharmacokinetics of dipeptidylpeptidase-4 inhibitors
AUTHOR(S): Scheen, A. J.
CORPORATE SOURCE: Division of Diabetes, Nutrition and Metabolic Disorders and Division of Clinical Pharmacology, Department of Medicine, CHU Sart Tilman, University of Liege, Liege, Belg.
SOURCE: Diabetes, Obesity and Metabolism (2010), 12(8), 648-658
CODEN: DOMEF6; ISSN: 1462-8902
PUBLISHER: Wiley-Blackwell
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 30 Aug 2010
AB A review. Type 2 diabetes (T2DM) is a complex disease combining defects in insulin secretion and insulin action. New compds. have been developed for improving glucose-induced insulin secretion and glucose control, without inducing hypoglycemia or weight gain. Dipeptidylpeptidase-4 (DPP-4) inhibitors are new oral glucose-lowering agents, so-called incretin enhancers, which may be used as monotherapy or in combination with other antidiabetic compds. Sitagliptin, vildaglipin and saxagliptin are already

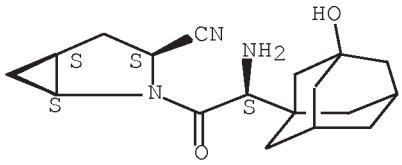
on the market in many countries, either as single agents or in fixed-dose combined formulations with metformin. Other DPP-4 inhibitors, such as alogliptin and linagliptin, are currently in late phase of development. The present paper summarizes and compares the main pharmacokinetics (PK) properties, i.e., absorption, distribution, metabolism and elimination, of these five DPP-4 inhibitors. Available data were obtained in clin. trials performed in healthy young male subjects, patients with T2DM, and patients with either renal insufficiency or hepatic impairment. PK characteristics were generally similar in young healthy subjects and in middle-aged overweight patients with diabetes. All together gliptins have a good oral bioavailability which is not significantly influenced by food intake. PK/pharmacodynamics characteristics, i.e., sufficiently prolonged half-life and sustained DPP-4 enzyme inactivation, generally allow one single oral administration per day for the management of T2DM; the only exception is vildagliptin for which a twice-daily administration is recommended because of a shorter half-life. DPP-4 inhibitors are in general not substrates for cytochrome P 450 (except saxagliptin that is metabolized via CYP 3A4/A5) and do not act as inducers or inhibitors of this system. Several metabolites have been documented but most of them are inactive; however, the main metabolite of saxagliptin also exerts a significant DPP-4 inhibition and is half as potent as the parent compound Renal excretion is the most important elimination pathway, except for linagliptin whose metabolism in the liver appears to be predominant. PK properties of gliptins, combined with their good safety profile, explain why no dose adjustment is necessary in elderly patients or in patients with mild to moderate hepatic impairment. As far as patients with renal impairment are concerned, significant increases in drug exposure for sitagliptin and saxagliptin have been reported so that appropriate redns. in daily dosages are recommended according to estimated glomerular filtration rate. The PK characteristics of DPP-4 inhibitors suggest that these compds. are not exposed to a high risk of drug-drug interactions. However, the daily dose of saxagliptin should be reduced when coadministered with potent CYP 3A4 inhibitors. In conclusion, besides their pharmacodynamic properties leading to effective glucose-lowering effect without inducing hypoglycemia or weight gain, DPP-4 inhibitors show favorable PK properties, which contribute to a good efficacy/safety ratio for the management of T2DM in clin. practice.

IT 361442-04-8, Saxagliptin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmacokinetics of dipeptidylpeptidase-4 inhibitors)

RN 361442-04-8 HCAPLUS

CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.

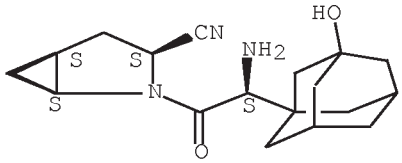


OS.CITING REF COUNT: 36 THERE ARE 36 CAPLUS RECORDS THAT CITE THIS RECORD (37 CITINGS)
REFERENCE COUNT: 76 THERE ARE 76 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 38 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2010:1054512 HCAPLUS Full-text
DOCUMENT NUMBER: 153:349696
TITLE: Saxagliptin: the evidence for its place in the treatment of type 2 diabetes mellitus
AUTHOR(S): Kulasa, Kristen; Edelman, Steven
CORPORATE SOURCE: Division of Endocrinology and Metabolism, VA San Diego Healthcare System, University of California, USA
SOURCE: Core Evidence (2010), 5, 23-37
CODEN: CEOVAF; ISSN: 1555-1741
URL: http://www.dovepress.com/getfile.php?fileID=7383
PUBLISHER: Dove Medical Press Ltd.
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English
ED Entered STN: 24 Aug 2010
AB A review. The worldwide prevalence of type 2 diabetes mellitus (T2DM) is high, and the chronically poor metabolic control that can result from T2DM is associated with a high risk for microvascular and macrovascular complications. Because of the progressive pathophysiol. of T2DM, oral antidiabetic agents often fail to provide sustained glycemic control, indicating the need for new therapies. Saxagliptin is an oral dipeptidyl peptidase-4 inhibitor, recently approved for the treatment of T2DM. Evidence review: Saxagliptin significantly improves glycemic control vs placebo, as demonstrated by decreasing glycated Hb, fasting plasma glucose, and postprandial plasma glucose levels when used as monotherapy; in initial combination with metformin; and as add-on therapy with metformin, sulfonylurea (SU), or thiazolidinedione (TZD). Saxagliptin also significantly improves β-cell function, is weight neutral, has a low risk for hypoglycemia, and has been shown to have cardiovascular safety. Place in therapy: The clin. profile for saxagliptin indicates that it is useful as an adjunct to diet and exercise as first-line monotherapy and in combination with metformin; or as add-on treatment for patients who cannot achieve glycemic control with a combination of diet and lifestyle changes and metformin, SU, or TZD.
IT 361442-04-8, Onglyza
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(clin. evidence on saxagliptin for the treatment of type 2 diabetes mellitus)

RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile,
2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-,
(1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.

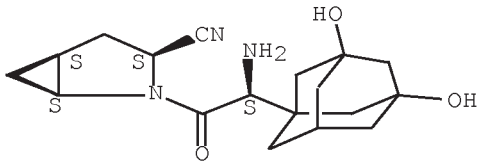


OS.CITING REF COUNT: 5 THERE ARE 5 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)
REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 39 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2010:970748 HCAPLUS Full-text
DOCUMENT NUMBER: 154:275051
TITLE: Saxagliptin: a new drug for the treatment of type 2 diabetes
AUTHOR(S): Thareja, Suresh; Aggarwal, Saurabh; Malla, Priyanka; Haksar, Diksha; Bhardwaj, Tilak Raj; Kumar, Manoj
CORPORATE SOURCE: University Institute of Pharmaceutical Sciences, Panjab University, Chandigarh, 160 014, India
SOURCE: Mini-Reviews in Medicinal Chemistry (2010), 10(8), 759-765
CODEN: MMCIAE; ISSN: 1389-5575
PUBLISHER: Bentham Science Publishers Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 05 Aug 2010
AB A review. Saxagliptin (BMS-477118), a recently FDA approved drug for the management of T2DM, has been developed by Bristol-Myers Squibb and AstraZeneca under the trade name Onglyza. Saxagliptin is a nitrile-containing selective, potent, reversible and durable DPP IV inhibitor developed as an alternative second-line to Metformin in place of a sulfonylurea. Saxagliptin increases and prolongs the action of incretin hormones by inhibiting the DPP IV enzyme that inactivates incretins usually within minutes. Saxagliptin is well absorbed and has low plasma protein binding and displays slow-binding properties to DPP IV. Saxagliptin is metabolized in vivo to form an active metabolite (BMS-510849), which is twofold less potent than the parent mol. The X-ray crystallog. revealed that Saxagliptin is covalently bound to the DPP IV active site. In drug-naive patients with T2DM and inadequate glycemic control, once-daily Saxagliptin monotherapy for 24 wks demonstrated clin. meaningful with no weight gain and was generally well tolerated.
IT 841302-24-7

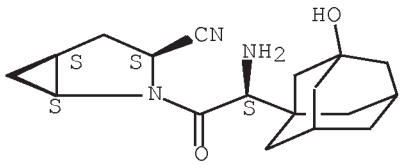
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(BMS 510849; Onglyza was metabolized to form active metabolite
BMS-510849 in drug-native patient with type 2 diabetes)
RN 841302-24-7 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile,
2-[(2S)-2-amino-2-(3,5-dihydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-,
(1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



IT 361442-04-8, Onglyza
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(Onglyza was well tolerated and effective for treatment of drug-native
patient with type 2 diabetes)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile,
2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-,
(1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD
(1 CITINGS)
REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 40 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2010:889550 HCAPLUS Full-text
DOCUMENT NUMBER: 154:100629
TITLE: Saxagliptin: new theraphy for type 2 diabetes
AUTHOR(S): Logan, Jill K.; Escano, Alisa K.
CORPORATE SOURCE: Department of Pharmacy, Inova Fairfax Hospital, Falls

Church, VA, USA
SOURCE: Journal of Pharmacy Technology (2010), 26(3), 123-128
CODEN: JPTEEB; ISSN: 8755-1225
PUBLISHER: Harvey Whitney Books Co.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 19 Jul 2010

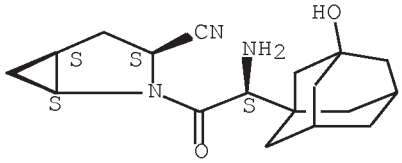
AB A review. Objective: To evaluate the efficacy of saxagliptin for the treatment of hyperglycemia associated with type 2 diabetes. Data Sources: A MEDLINE/PubMed search was conducted of all available date ranges from 1990 through Oct. 2009 for literature in the English language, using the search terms saxagliptin, type 2 diabetes mellitus, incretin hormones, and dipeptidyl peptidase-4 inhibitors. The manufacturer of saxagliptin (Onglyza) was contacted for clin. trial information. Study Selection: Five prospective, randomized controlled trials were reviewed. Studies were included in this review if they had examined saxagliptin and its effects on hyperglycemia. Trials examined included those on saxagliptin monotherapy and those on saxagliptin in combination with metformin, with a sulfonylurea, and with a thiazolidinedione. Data from the MEDLINE/PubMed search, as well as clin. trial data obtained from the manufacturer, were used in this review. Data Synthesis: Saxagliptin demonstrated statistically significant decreases of 0.43-0.54% in Hb A1c (A1C) in the monotherapy treatment group. The A1C-lowering effects were the greatest, with a decrease of 2.5% in patients concomitantly administered metformin and saxagliptin as initial therapy. In addition to its effects on A1C, saxagliptin proved to be weight neutral and had minimal risks of hypoglycemia, with hypoglycemia seen only in the saxagliptin in combination with a sulfonylurea group. Conclusions: Saxagliptin is an effective treatment for hyperglycemia associated with type 2 diabetes. It is currently a third-line option in the American Diabetes Association treatment algorithm for type 2 diabetes and, based on the trials reviewed here, this is an acceptable place in therapy. Saxagliptin is a good option for patients with diabetes who are at high risk of hypoglycemia.

IT 361442-04-8, Saxagliptin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(saxagliptin may be effective in treatment of patient with hyperglycemia associated to type 2 diabetes mellitus)

RN 361442-04-8 HCAPLUS

CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

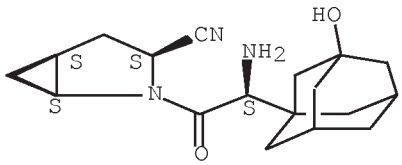
Absolute stereochemistry.



REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 41 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2010:860078 HCAPLUS Full-text
DOCUMENT NUMBER: 154:426493
TITLE: Incretin-based therapies for type 2 diabetes mellitus: current status and future prospects
AUTHOR(S): Drab, Scott R.
CORPORATE SOURCE: University of Pittsburgh School of Pharmacy, Pittsburgh, PA, USA
SOURCE: Pharmacotherapy (2010), 30(6), 609-624
CODEN: PHPYDQ; ISSN: 0277-0008
PUBLISHER: Pharmacotherapy Publications
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 12 Jul 2010
AB A review. Incretin-based therapies encompass two new classes of antidiabetic drugs: glucagon-like peptide-1 (GLP-1) receptor agonists (e.g., liraglutide, exenatide, and exenatide long-acting release), which are structurally related to GLP-1, and the dipeptidyl peptidase-4 (DPP-4) inhibitors (e.g., sitagliptin and saxagliptin), which limit the breakdown of endogenous GLP-1. To evaluate the safety and effectiveness of incretin-based therapies for the treatment of type 2 diabetes mellitus and the role of these therapies in clin. practice, a MEDLINE search (Jan. 1985-Nov. 2009) was conducted. Relevant refs. from the publications identified were also reviewed. Of 28 studies identified, 22 were randomized controlled trials. Data show that these therapies affect insulin secretion in a glucose-dependent manner, achieving clin. meaningful redns. in Hb A1c levels, with very low rates of hypoglycemia. In addition, redns. in body weight have been observed with GLP-1 receptor agonists, which also exert a pronounced effect on systolic blood pressure. Various human and animal studies show that GLP-1 improves β-cell function and increases β-cell proliferation in vitro, which may slow disease progression. Thus, incretin-based therapies represent a promising addition to the available treatments for type 2 diabetes.
IT 361442-04-8, Saxagliptin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(saxagliptin may be safe and effective in treatment of patient with type 2 diabetes mellitus)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.

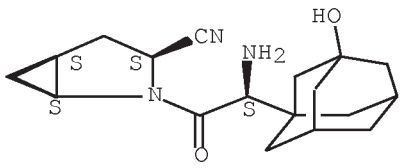


OS.CITING REF COUNT: 16 THERE ARE 16 CAPLUS RECORDS THAT CITE THIS RECORD (16 CITINGS)
REFERENCE COUNT: 110 THERE ARE 110 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 42 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2010:757641 HCAPLUS Full-text
DOCUMENT NUMBER: 154:54885
TITLE: Diabesity: therapeutic options
AUTHOR(S): Colagiuri, S.
CORPORATE SOURCE: Boden Institute of Obesity, Nutrition and Exercise, University of Sydney, Sydney, NSW, Australia
SOURCE: Diabetes, Obesity and Metabolism (2010), 12(6), 463-473
CODEN: DOMEF6; ISSN: 1462-8902
PUBLISHER: Wiley-Blackwell
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 18 Jun 2010
AB A review. A pathogenic relationship exists between type 2 diabetes and obesity. Over the last decade, the escalation in diabetes cases has paralleled the rapid increase in obesity rates, constituting a global health crisis. Environmental risk factors attributed to the global increase in obesity include the consumption of high-calorie, high-fat foods and inadequate phys. activity. Obese individuals may also have a genetic predisposition for obesity. Both diabetes and obesity confer an elevated risk of developing a range of complications and comorbidities, including cardiovascular disease, hypertension and stroke, which can complicate disease management. This review examines the etiol. of the linkages between diabetes and obesity and the range of available therapies. Recent clin. evidence substantiating the efficacy and safety of incretin-based antidiabetic therapies is analyzed, in addition to data on antiobesity therapeutic strategies, such as antiobesity agents, behavior modification and bariatric surgery. Glucose control is often accompanied by weight-neutral or modest weight reduction effects with DPP-4 inhibitor treatment (sitagliptin, vildagliptin, saxagliptin) and weight loss with GLP-1 receptor agonist therapy (exenatide, liraglutide). Studies of antiobesity agents including orlistat, sibutramine and rimonabant have shown attrition rates of 30-40%, and the long-term effects of these agents remain unknown. Bariatric surgical procedures commonly performed are laparoscopic adjustable banding of the stomach and the Roux-en-Y gastric bypass, and have produced type 2 diabetes remission rates of up to 73%. Therapeutic strategies that integrate glycemic control and weight loss will assume greater importance as the prevalence of diabetes and obesity increase.
IT 361442-04-8, Saxagliptin
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(therapeutic options for diabesity)
RN 361442-04-8 HCAPLUS
CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile,

2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 7 THERE ARE 7 CAPLUS RECORDS THAT CITE THIS RECORD (7 CITINGS)
REFERENCE COUNT: 144 THERE ARE 144 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 43 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2010:702461 HCAPLUS Full-text
DOCUMENT NUMBER: 153:609405
TITLE: Dipeptidyl peptidase-4 inhibitors for the treatment of type 2 diabetes mellitus
AUTHOR(S): Neumiller, Joshua J.; Wood, Lindy; Campbell, R. Keith
CORPORATE SOURCE: Department of Pharmacotherapy and Elder Services, Washington State University, Spokane, WA, USA
SOURCE: Pharmacotherapy (2010), 30(5), 463-484
CODEN: PHPYDQ; ISSN: 0277-0008
PUBLISHER: Pharmacotherapy Publications
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
ED Entered STN: 08 Jun 2010
AB A review. Type 2 diabetes mellitus traditionally has been characterized by insulin resistance and β-cell dysfunction, leading to hyperglycemia and eventual micro- and macrovascular complications. Dipeptidyl peptidase-4 (DPP-4) inhibitors are a relatively new class of drugs available for the management of type 2 diabetes. In order to provide a comprehensive evaluation and comparison of the pharmacol., pharmacokinetics, efficacy, and safety of the DPP-4 inhibitors-sitagliptin, vildagliptin, saxagliptin, and alogliptin-in the treatment of type 2 diabetes, we conducted a MEDLINE search (1966-July 2009) for pertinent English-language articles. Abstrs. of the annual meetings of the American Diabetes Association and European Association for the Study of Diabetes from 2005-2009 were also searched. As a drug class, the DPP-4 inhibitors have become widely accepted in clin. practice because of their low risk of hypoglycemia, favorable adverse-effect profile, and once-daily dosing. They are weight neutral (do not cause weight gain or loss) and appear to decrease β-cell apoptosis and increase β-cell survival. Because clin. studies directly comparing agents from this class have not, to our knowledge, been conducted, making comparisons in terms of efficacy and safety will become difficult for clinicians as more agents

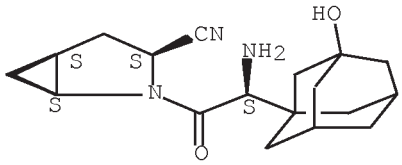
become available. Based on information from preclin., clin., and postmarketing data, there does not appear to be a compelling advantage of one DPP-4 inhibitor over another in terms of efficacy, safety, or ease of clin. use. Although theor. advantages exist for agents with a higher specificity for DPP-4 inhibition vs. inhibition of other isoenzymes associated with toxicity, comparative studies and/or increased clin. experience with this class of drug will determine the clin. advantages, if any, of one agent over another.

IT 361442-04-8, Saxagliptin
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(dipeptidyl peptidase-4 inhibitors for the treatment of type 2 diabetes mellitus)

RN 361442-04-8 HCAPLUS

CN 2-Azabicyclo[3.1.0]hexane-3-carbonitrile, 2-[(2S)-2-amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-, (1S,3S,5S)- (CA INDEX NAME)

Absolute stereochemistry.



OS.CITING REF COUNT: 23 THERE ARE 23 CAPLUS RECORDS THAT CITE THIS RECORD (23 CITINGS)
REFERENCE COUNT: 143 THERE ARE 143 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L49 ANSWER 44 OF 87 HCAPLUS COPYRIGHT 2012 ACS on STN
ACCESSION NUMBER: 2010:661501 HCAPLUS Full-text
DOCUMENT NUMBER: 153:163056
TITLE: Role of saxagliptin as monotherapy or adjunct therapy in the treatment of type 2 diabetes
AUTHOR(S): Sharma, Morali D.
CORPORATE SOURCE: Baylor College of Medicine, Houston, TX, USA
SOURCE: Therapeutics and Clinical Risk Management (2010), 6, 233-237
CODEN: TCRMA6; ISSN: 1178-203X
URL: http://www.dovepress.com/getfile.php?fileID=6268
PUBLISHER: Dove Medical Press Ltd.
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English
ED Entered STN: 30 May 2010
AB A review. Type 2 diabetes is associated with decreased incretin hormone response to an oral glucose load, and a progressive decline in postprandial