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APPLICATION NUMBER	FILING OR 371 (c) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
10/129,773	08/28/2002	Alan Roy Dearn	Z70617-1US

CONFIRMATION NO. 7672

OC000000019826829

44992
ASTRAZENECA R&D BOSTON
35 GATEHOUSE DRIVE
WALTHAM, MA 02451-1215

Date Mailed: 07/31/2006

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 07/17/2006.

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.

MBeyene

MELKAM BEYENE
PTOSS (703) 305-3006

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APPLICATION NUMBER	FILING OR 371 (c) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
10/129,773	08/28/2002	Alan Roy Dearn	ASZD-P01-617

CONFIRMATION NO. 7672

OC000000019826776

28120
FISH & NEAVE IP GROUP
ROPES & GRAY LLP
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

Date Mailed: 07/31/2006

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 07/17/2006.

- The Power of Attorney to you in this application has been revoked by the assignee who has intervened as provided by 37 CFR 3.71.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).

MELKAM BEYENE
PTOSS (703) 305-3006

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IFW

PTO/SB/82 (04-05)
Approved for use through 11/30/2005. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

REVOCATION OF POWER OF ATTORNEY WITH NEW POWER OF ATTORNEY AND CHANGE OF CORRESPONDENCE ADDRESS

Application Number	10/129773
Filing Date	August 28, 2002
First Named Inventor	Alan Roy Dearn
Art Unit	N/A
Examiner Name	Not Yet Assigned
Attorney Docket Number	Z70617-1US

I hereby revoke all previous powers of attorney given in the above-identified application.

[ ] A Power of Attorney is submitted herewith.

OR

[x] I hereby appoint the practitioners associated with the Customer Number: 44992

[x] Please change the correspondence address for the above-identified application to:

[x] The address associated with Customer Number: 44992

OR

[x] Firm or Individual Name	AstraZeneca Pharmaceuticals LP				
Address	Global Intellectual Property 35 Gatehouse Drive				
City	Waltham				
Country	US	State	MA	Zip	02451
Telephone	(781) 839-4000	Email			

I am the:

[ ] Applicant/Inventor.

[x] Assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)

SIGNATURE of Applicant or Assignee of Record

Signature			
Name	Kevin Bill		
Date	6 July 2006	Telephone	+44 (0)1625 512461

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

[x] *Total of 1 forms are submitted.

I hereby certify that this correspondence is being deposited with the U.S. Postal Service with sufficient postage as First Class Mail, in an envelope addressed to: MS Post Issue, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date shown below.

Dated: 7-13-06 Signature: Maura A. Gallagher /Maura A. Gallagher

PTO/SB/96 (09-04)
Approved for use through 07/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Dearn et al.

Application No./Patent No.: 6750237 Filed/Issue Date: June 15, 2006

Entitled: PHARMACEUTICAL FORMULATIONS CONTAINING ZOLMITRIPTAN

AstraZeneca AB , a Corporation
(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that it is:

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

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

A. [x] An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 012996 , Frame 0425 , or for which a copy thereof is attached.

OR

B. [ ] A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as shown below:

1. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at Reel _____ , Frame _____ , or for which a copy thereof is attached.
2. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at Reel _____ , Frame _____ , or for which a copy thereof is attached.
3. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at Reel _____ , Frame _____ , or for which a copy thereof is attached.

[ ] Additional documents in the chain of title are listed on a supplemental sheet.

[ ] Copies of assignments or other documents in the chain of title are attached.
[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, if the assignment is to be recorded in the records of the USPTO. See MPEP 302.08]

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

Signature — 6 July 2006 Date

Kevin Bill — +44 (0)1625 512461
Printed or Typed Name — Telephone Number

Authorized Signer for Assignee
Title

I hereby certify that this correspondence is being deposited with the U.S. Postal Service with sufficient postage as First Class Mail, in an envelope addressed to: MS Post Issue, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date shown below.

Dated: 7-13-06 Signature: Maura A. Gallagher Maura A. Gallagher

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (703) 746-4000

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 4 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Legibly mark-up with any corrections or use Block 1)

28120 7590 02/27/2004

ROPES & GRAY LLP
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

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

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

Mary Jane DiPalma (Depositor's name)
(Signature)
April 29, 2004 (Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/129,773	08/28/2002	Alan Roy Deam	ASZD-P01-617	7672

TITLE OF INVENTION: PHARMACEUTICAL FORMULATIONS CONTAINING ZOLMITRIPTAN

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1330	$0	$1330	05/27/2004

EXAMINER	ART UNIT	CLASS-SUBCLASS
PRYOR, ALTON NATHANIEL	1616	514-376000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

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

1 Ropes & Gray LLP
2
3

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

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. Inclusion of assignee data is only appropriate when an assignment has been previously submitted to the USPTO or is being submitted under separate cover. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: AstraZeneca AB

(B) RESIDENCE: (CITY and STATE OR COUNTRY): London, United Kingdom

Please check the appropriate assignee category or categories (will not be printed on the patent); ☐ individual ☑ corporation or other private group entity ☐ government

4a. The following fee(s) are enclosed:

☒ Issue Fee
☐ Publication Fee
☒ Advance Order - # of Copies 10

4b. Payment of Fee(s):

☐ A check in the amount of the fee(s) is enclosed.
☐ Payment by credit card. Form PTO-2038 is attached.
☒ The Director is hereby authorized by charge the required fee(s), or credit any overpayment, to Deposit Account Number 18-1945 (enclose an extra copy of this form).

Director for Patents is requested to apply the Issue Fee and Publication Fee (if any) or to re-apply any previously paid issue fee to the application identified above.

(Authorized Signature) (Date)
April 29, 2004

NOTE; The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

05/05/2004 MAHMED2 00000088 181945 10129773
01 FC:1501 1330.00 DA
02 FC:8001 30.00 DA

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, Alexandria, Virginia 22313-1450.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

TRANSMIT THIS FORM WITH FEE(S)

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

NOTICE OF ALLOWANCE AND FEE(S) DUE

28120 7590 02/27/2004

ROPES & GRAY LLP
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER	
PRYOR, ALTON NATHANIEL	
ART UNIT	**PAPER NUMBER**
1616	

DATE MAILED: 02/27/2004

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/129,773	08/28/2002	Alan Roy Dearn	ASZD-P01-617	7672

TITLE OF INVENTION: PHARMACEUTICAL FORMULATIONS CONTAINING ZOLMITRIPTAN

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1330	$0	$1330	05/27/2004

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

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE REFLECTS A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE APPLIED IN THIS APPLICATION. THE PTOL-85B (OR AN EQUIVALENT) MUST BE RETURNED WITHIN THIS PERIOD EVEN IF NO FEE IS DUE OR THE APPLICATION WILL BE REGARDED AS ABANDONED.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:
A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status is changed, pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above and notify the United States Patent and Trademark Office of the change in status, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check the box below and enclose the PUBLICATION FEE and 1/2 the ISSUE FEE shown above.

☐ Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

II. PART B - FEE(S) TRANSMITTAL should be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). Even if the fee(s) have already been paid, Part B - Fee(s) Transmittal should be completed and returned. If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted.

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

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

PTOL-85 (Rev. 11/03) Approved for use through 04/30/2004.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (703) 746-4000

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 4 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Legibly mark-up with any corrections or use Block 1)

28120 7590 02/27/2004

ROPES & GRAY LLP
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

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

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

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/129,773	08/28/2002	Alan Roy Dearn	ASZD-P01-617	7672

TITLE OF INVENTION: PHARMACEUTICAL FORMULATIONS CONTAINING ZOLMITRIPTAN

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1330	$0	$1330	05/27/2004

EXAMINER	ART UNIT	CLASS-SUBCLASS
PRYOR, ALTON NATHANIEL	1616	514-376000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

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

1 _____
2 _____
3 _____

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

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. Inclusion of assignee data is only appropriate when an assignment has been previously submitted to the USPTO or is being submitted under separate cover. Completion of this form is NOT a substitute for filing an assignment.

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

Please check the appropriate assignee category or categories (will not be printed on the patent); ❑ individual ❑ corporation or other private group entity ❑ government

4a. The following fee(s) are enclosed:

❑ Issue Fee
❑ Publication Fee
❑ Advance Order - # of Copies _____

4b. Payment of Fee(s):

❑ A check in the amount of the fee(s) is enclosed.
❑ Payment by credit card. Form PTO-2038 is attached.
❑ The Director is hereby authorized by charge the required fee(s), or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

Director for Patents is requested to apply the Issue Fee and Publication Fee (if any) or to re-apply any previously paid issue fee to the application identified above.

(Authorized Signature) (Date)

NOTE; The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

TRANSMIT THIS FORM WITH FEE(S)

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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/129,773	08/28/2002	Alan Roy Dearn	ASZD-P01-617	7672

28120 7590 02/27/2004

ROPES & GRAY LLP
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER	
PRYOR, ALTON NATHANIEL	
ART UNIT	**PAPER NUMBER**
1616	

DATE MAILED: 02/27/2004

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

The Patent Term Adjustment to date is 0 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 0 day(s).

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

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

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (703) 305-1383. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at (703) 305-8283.

PTOL-85 (Rev. 11/03) Approved for use through 04/30/2004.

Notice of Allowability	Application No.	Applicant(s)	
	10/129,773	DEARN ET AL.	
	Examiner	Art Unit	
	Alton N. Pryor	1616	

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

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

1. ☐ This communication is responsive to *11/28/03*.

2. ☐ The allowed claim(s) is/are *1-12,15,16,18,21 (claims renumbered 1-16)*.

3. ☐ The drawings filed on _____ are accepted by the Examiner.

4. ☐ 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 the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

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

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

6. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

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

Authorization for this examiner's amendment was given in a telephone interview with Attorney Halstead on 2/20/04.

The application has been amended as follows:

a) In claim 15 line 2 delete "and" and insert --- or ---.

The following is an examiner's statement of reasons for allowance: The prior art does not teach or suggest a composition comprising zolmitriptan existing in a pH ranging from 4.5 to 5.5.

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

Telephonic Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alton N. Pryor whose telephone number is 571-272-0621. The examiner can normally be reached on 8:00 a.m. - 4:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page can be reached on 571-272-0612. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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).

ALTON N. PRYOR
PRIMARY EXAMINER

Alton Pryor
Primary Examiner
AU 1616

Issue Classification	Application No.	Applicant(s)	
	10/129,773	DEARN ET AL.	
	Examiner	Art Unit	
	Alton N. Pryor	1616	

ISSUE CLASSIFICATION

ORIGINAL CLASS	ORIGINAL SUBCLASS	CROSS REFERENCE(S) CLASS	CROSS REFERENCE(S) SUBCLASS (ONE SUBCLASS PER BLOCK)
514	376	548	122

INTERNATIONAL CLASSIFICATION

A01N	43/76
C07D	419/00
	/
	/
	/

(Assistant Examiner) (Date)

(Legal Instruments Examiner) (Date)

Alton N. Pryor
ALTON N. PRYOR
PRIMARY EXAMINER
1616
(Primary Examiner) 2/20/04 (Date)

Total Claims Allowed: 16

O.G. Print Claim(s)	O.G. Print Fig.
1	—

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

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
	1		31		61		91		121		151		181
	2		32		62		92		122		152		182
	3		33		63		93		123		153		183
	4		34		64		94		124		154		184
9	5		35		65		95		125		155		185
11	6		36		66		96		126		156		186
5	7		37		67		97		127		157		187
6	8		38		68		98		128		158		188
7	9		39		69		99		129		159		189
8	10		40		70		100		130		160		190
10	11		41		71		101		131		161		191
12	12		42		72		102		132		162		192
	13		43		73		103		133		163		193
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	22		52		82		112		142		172		202
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	30		60		90		120		150		180		210

Index of Claims

Application No.	Applicant(s)
10/129,773	DEARN ET AL.
Examiner	**Art Unit**
Alton N. Pryor	1616

√	Rejected	–	(Through numeral) Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

Claim		Date
Final	Original	2 20 04
1	1	=
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7	9	=
8	10	=
10	11	=
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Search Notes

Application No.	Applicant(s)	
10/129,773	DEARN ET AL.	
Examiner	**Art Unit**	
Alton N. Pryor	1616	

SEARCHED			
Class	Subclass	Date	Examiner
514	376	2/19/2004	ANP
548	122	2/20/2004	ANP

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner
514	376	2/20/04	ANP
548	122	2/20/04	ANP

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR
STN	2/23/04	ANP

In the claims:

For the convenience of the Examiner, all claims being examined, whether or not amended, are presented below.

1. (Currently Amended) A pharmaceutical formulation suitable for intranasal administration which comprises zolmitriptan and a pharmaceutically acceptable carrier wherein the pH of the formulation is ~~less than 7.0.~~ in the range 4.5 to 5.5.

2. (Currently Amended) A pharmaceutical formulation according to claim 1, wherein the pH of the formulation is ~~in the range 4.5 to 5.5.~~ 5.

3. (Previously Presented) A pharmaceutical formulation according to claim 1 wherein the formulation is buffered.

4. (Previously Presented) A pharmaceutical formulation according to claim 2 wherein the formulation is buffered.

5. (Currently Amended) ~~A pharmaceutical formulation according to claim 3~~ A pharmaceutical formulation suitable for intranasal administration which comprises zolmitriptan and a pharmaceutically acceptable carrier wherein the pH of the formulation is less than 7.0, wherein the formulation is buffered by ~~wherein the buffer is~~ a mixture of citric acid and disodium phosphate.

6. (Currently Amended) ~~A pharmaceutical formulation according to claim 4~~ A pharmaceutical formulation suitable for intranasal administration which comprises zolmitriptan and a pharmaceutically acceptable carrier wherein the pH of the formulation is in the range 4.5 to 5.5, wherein the formulation is buffered by ~~wherein the buffer is~~ a mixture of citric acid and disodium phosphate.

7. (Previously Presented) A pharmaceutical formulation according to claim 1 which is sterile.

8. (Previously Presented) A pharmaceutical formulation according to claim 2 which is sterile.

7

~~9.~~ (Previously Presented) A pharmaceutical formulation according to claim 3 which is sterile.

8

~~10.~~ (Previously Presented) A pharmaceutical formulation according to claim 4 which is sterile.

10 9

~~11.~~ (Previously Presented) A pharmaceutical formulation according to claim ~~5~~ which is sterile.

11

~~12.~~ (Previously Presented) A pharmaceutical formulation according to claim ~~6~~ which is sterile.

13. (Cancelled) A process for preparing a sterile pharmaceutical formulation as defined in any one of claims 7-12 which comprises autoclaving.

14. (Cancelled) A method of treating a disease condition wherein agonism of 5HT1-receptors is beneficial which comprises administering an effective amount of a pharmaceutical formulation as defined in any one of claims 1 to 12.

13

~~15.~~ (Currently Amended) An intranasal administration device containing a pharmaceutical formulation as defined in any one of claims 1[to 12], 2, ~~3~~ 9 and ~~6~~ 11.

14 13

~~16.~~ (Currently Amended) ~~An~~ The intranasal administration device of claim ~~15~~, wherein the ~~containing a~~ pharmaceutical formulation ~~as defined in any one of claims 1 to 12~~ is packaged to ~~provide~~ protect~~ion~~ the formulation from light.

17. (Cancelled)

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~~18.~~ (Currently Amended) An aqueous solution of zolmitriptan in a buffer at a pH in the range of 4.5 to 5.5.

19. (Cancelled)

20. (Cancelled)

16 15

~~21~~. (New) The aqueous solution of claim ~~18~~, wherein the pH is 5.

PHARMACEUTICAL FORMULATIONS CONTAINING ZOLMITRIPTAN

The present invention relates to new pharmaceutical formulations, their preparation and their use in treatment of disease. In particular the present invention relates to pharmaceutical formulations of the anti-migraine drug zolmitriptan for nasal application.

Zolmitriptan has the chemical name (S)-4-{{3-[2-(dimethylaminoethyl]-1H-indol-5-yl]methyl]-2-oxazolidinone. Zolmitriptan is a selective 5HT1-receptor agonist. The 5HT1-receptor mediates vasoconstriction and thus modifies blood flow to the carotid vascular bed. 5HT1-receptor agonists are beneficial in the treatment (including prophylaxis) of disease conditions wherein vasoconstriction in the carotid vascular bed is indicated, for example migraine, cluster headache and headache associated with vascular disorders, hereinafter referred to collectively as 'migraine'. Zolmitriptan has been developed for the acute treatment of migraine in the form of a 2.5 mg and 5 mg tablet intended to be taken up to a maximum of 15 mg per day.

Although zolmitriptan is a successful drug of considerable benefit to migraine sufferers, there is a continuing need for alternative methods for the direct treatment of migraine and the prophylactic treatment of migraine. In particular, patients suffering from migraine or the onset of migraine need fast relief of their suffering.

Zolmitriptan is a member of a class of drugs known as triptans, for example sumatriptan, naratriptan and rizatriptan, which are prescribed for the treatment of migraine. The leader in terms of sales is sumitriptan which has been marketed as an oral formulation. A subcutaneous formulation was also developed; this was more efficacious (P. Tfelt-Hansen, Cephalalgia 1998, Vol 18(8), page 532-8) and gave a faster onset of action but was not so acceptable to the patient. An intranasal spray was also developed. This was more user-friendly than the subcutaneous injection but was reported to be less effective in reducing the symptoms of migraine attacks (C Dahlof, Cephalalgia 1998; 18(5): 278-282). Also, many patients reported an unpleasant bitter taste after using the nasal spray.

The present inventors sought a formulation of zolmitriptan that achieved fast relief whilst maintaining high efficacy. They also sought a formulation that, for the wide variety of patients that suffer from migraines, had a more acceptable route of administration than a subcutaneous injection. Clearly, the thought of a subcutaneous injection may dissuade many patients from taking appropriate and necessary treatment. Furthermore, the inventors sought

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     (FILE 'HOME' ENTERED AT 15:02:45 ON 23 FEB 2004)

     FILE 'REGISTRY' ENTERED AT 15:02:56 ON 23 FEB 2004
L1             1 S ZOLMITRIPTAN/CN

     FILE 'CAPLUS, USPATFULL' ENTERED AT 15:03:41 ON 23 FEB 2004
L2           274 S L1
L3            41 S L1 AND PH
L4             0 S L1 (P) (ACIDIC OR PH)
L5             2 S L1 (P) (ACID? OR PH)
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41

1616

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Dearn et al.

Serial No: 10/129773

Filed: August 28, 2002

For: PHARMACEUTICAL FORMULATIONS CONTAINING ZOLMITRIPTAN

Attorney Docket No. ASZD-P01-617

Art Unit: 1616

Examiner: Alton N. Pryor

CERTIFICATE OF MAILING UNDER 37 C.F.R. §1.8(a)

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail, postage prepaid, in an envelope addressed to: Mail Stop Non-Fee Amendments, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 on the date indicated below:

November 24, 2003
Date of Signature
and of Mail Deposit

Mary Jane DiPalma

MS Non-Fee Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REPLY UNDER 37 CFR 1.111

Sir:

This amendment is being filed in reply to the outstanding Office Action, mailed August 26, 2003, in connection with the above application. Please enter the following amendments:

In the claims:

For the convenience of the Examiner, all claims being examined, whether or not amended, are presented below.

1. (Currently Amended) A pharmaceutical formulation suitable for intranasal administration which comprises zolmitriptan and a pharmaceutically acceptable carrier wherein the pH of the formulation is ~~less than 7.0.~~ in the range 4.5 to 5.5.

2. (Currently Amended) A pharmaceutical formulation according to claim 1, wherein the pH of the formulation is ~~in the range 4.5 to 5.5.~~ 5.

3. (Previously Presented) A pharmaceutical formulation according to claim 1 wherein the formulation is buffered.

4. (Previously Presented) A pharmaceutical formulation according to claim 2 wherein the formulation is buffered.

5. (Currently Amended) ~~A pharmaceutical formulation according to claim 3~~ A pharmaceutical formulation suitable for intranasal administration which comprises zolmitriptan and a pharmaceutically acceptable carrier wherein the pH of the formulation is less than 7.0, wherein the formulation is buffered by ~~wherein the buffer is~~ a mixture of citric acid and disodium phosphate.

6. (Currently Amended) ~~A pharmaceutical formulation according to claim 4~~ A pharmaceutical formulation suitable for intranasal administration which comprises zolmitriptan and a pharmaceutically acceptable carrier wherein the pH of the formulation is in the range 4.5 to 5.5, wherein the formulation is buffered by ~~wherein the buffer is~~ a mixture of citric acid and disodium phosphate.

7. (Previously Presented) A pharmaceutical formulation according to claim 1 which is sterile.

8. (Previously Presented) A pharmaceutical formulation according to claim 2 which is sterile.

9. (Previously Presented) A pharmaceutical formulation according to claim 3 which is sterile.

10. (Previously Presented) A pharmaceutical formulation according to claim 4 which is sterile.

11. (Previously Presented) A pharmaceutical formulation according to claim 5 which is sterile.

12. (Previously Presented) A pharmaceutical formulation according to claim 6 which is sterile.

13. (Cancelled) A process for preparing a sterile pharmaceutical formulation as defined in any one of claims 7-12 which comprises autoclaving.

14. (Cancelled) A method of treating a disease condition wherein agonism of 5HT1-receptors is beneficial which comprises administering an effective amount of a pharmaceutical formulation as defined in any one of claims 1 to 12.

15. (Currently Amended) An intranasal administration device containing a pharmaceutical formulation as defined in any one of claims 1[to 12], 2, 5 and 6.

16. (Currently Amended) ~~An~~ The intranasal administration device of claim 15, wherein the ~~containing a~~ pharmaceutical formulation ~~as defined in any one of claims 1 to 12~~ is packaged to ~~provide~~ protect~~ion~~ the formulation from light.

17. (Cancelled)

18. (Currently Amended) An aqueous solution of zolmitriptan in a buffer at a pH in the range of 4.5 to 5.5.

19. (Cancelled)

20. (Cancelled)

21. (New) The aqueous solution of claim 18, wherein the pH is 5.

REMARKS

The Examiner states that claims 1-14 are pending. Applicants respectfully submit that claims 1-20 were pending. A substitute specification containing 20 claims was filed and received by the USPTO on May 9, 2002 at the time of national entry. The Examiner appears to have examined the 14 claims appearing in the parent PCT application, rather than the 20 claims found in the substitute specification of the subject application. Accordingly, Applicants will indicate in the remarks which pending claims correspond to those examined by the Examiner.

Applicants have cancelled claims 14, 17, 19 and 20, and added new claim 21. Thus, claims 1-13, 16, 18 and 21 are pending.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

A. Objected claims

Examined claims 5-10 were objected to as being in improper form because a multiple dependent claim cannot depend from another multiple dependent claim. Applicants note that claim 5 has been rewritten as claims 7-12, which are singly dependent claim. Examined claims 6 and 7, corresponding to pending claims 13 and 14, have been cancelled. Examined claims 9 and 10, corresponding to pending claims 15 and 16, have been amended to depend from independent or singly dependent claims. Examined claim 8 does not have a corresponding pending claim among the pending claims. Accordingly, Applicants respectfully request that the Examiner withdraw this ground of rejection.

B. Claim Rejections under 35 USC §102

Claims 13 and 14 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Robertson and Penkler. Without conceding the correctness of the Office Action's position but to expedite prosecution, Applicants have cancelled claims directed to this subject matter. Accordingly, Applicants respectfully request that the Examiner withdraw this ground of rejection.

C. Claim Rejections under 35 USC §103

Claims 1, 3, and 11 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Robertson and Penkler. Without conceding the correctness of the Office Action's position but to expedite prosecution, Applicants have amended claim 1 to incorporate the language of claim 2, which the Examiner indicated as allowable if written in independent form including all the limitations of each base claim and intervening claim. Accordingly, Applicants submit that claim 1 is allowable, and that the claims dependent thereon are similarly allowable. Accordingly, Applicants respectfully request that the Examiner withdraw this ground of rejection.

D. Allowable Matter

Applicants acknowledge that the Examiner found claim 12 (corresponding to pending claim 18) allowable. On page 4, 1st full paragraph, lines 3-4, Applicants believe the Examiner meant to say "Claim 12 is allowable. The prior art does [not] teach or suggest..." Pending claim 18 corresponds to this subject matter, and therefore should be allowable.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945**.

Respectfully Submitted,

Date: November 24, 2003

David P. Halstead
Reg. No. 44,735

Customer No: 28120
Docketing Specialist
Ropes & Gray LLP
One International Place
Boston, MA 02110
Phone: 617-951-7000
Fax: 617-951-7050

UNITED STATES PATENT AND TRADEMARK OFFICE

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United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/129,773	08/28/2002	Alan Roy Dearn	ASZD-P01-617	7672

28120 7590 08/26/2003

ROPES & GRAY LLP
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER
PRYOR, ALTON NATHANIEL

ART UNIT	PAPER NUMBER
1616	

DATE MAILED: 08/26/2003

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

Offic Action Summary	Application No. 10/129,773	Applicant(s) DEARN ET AL.	
	Examiner Alton N. Pryor	Art Unit 1616	

-- Th MAILING DATE of this communication appears on the cov r sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) 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 the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- 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 _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *12* is/are allowed.

6)☒ Claim(s) *1-4,11,13 and 14* is/are rejected.

7)☒ Claim(s) *5-10* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

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.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

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-1449) Paper No(s) *3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Objected to Claims under 37 CFR 1.75(c)

Claims 5-10 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from another multiple dependent claim. See MPEP § 608.01(n). Accordingly, the claims 5-10 have not been further treated on the merits.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 13 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Robertson et al (EP 636623; 1/2/95). Robertson teaches the citrate salt of zolmitriptan in aqueous solution. Page 4 lines 18-27.

Claims 13 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Penkler et al (WO 9802186; 1/22/98). Penkler teaches the citrate salt of zolmitriptan in aqueous solution. See page 5 4th complete paragraph.

Claim Rejections - 35 USC § 103

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

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1,3,11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Robertson above. Robertson teaches an aqueous intranasal composition comprising zolmitriptan and water as a pharmaceutically acceptable carrier. Robertson teaches that the composition is buffered at pH 7.0. See page 4 lines 18-30, page 5 lines 2-41, page 18 lines 17-44, page 29 line 45 – page 30 line 34.Robertson does not teach the composition having a pH of less than 7. However, it would have been obvious, in the absence of unexpected results, to make the prior art composition having a pH slightly less than 7 (e.g. pH = 6.9). One would have been motivated to do this because one having ordinary skill in the art would know that a slight change in pH would not drastically affect the physical / chemical properties of the composition.

Claims 1,3,11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Penkler above. Penkler teaches an aqueous intranasal composition comprising zolmitriptan and water as a pharmaceutically acceptable carrier. Penkler teaches that the composition is buffered at pH 7.4. Penkler teaches the presence of phosphate buffer for pH control. See page 2 3rd complete paragraph, page 5 3rd complete paragraph, page 6 4th complete paragraph, page 7 6th complete paragraph, page 8 2nd complete paragraph – page 9 2nd complete paragraph, page 10 1st complete paragraph. Penkler does not teach the composition having a pH of less than 7.0. However, it would have been obvious, in the absence of unexpected results, to make the prior art composition having a pH slightly less than 7.0 (e.g. pH = 6.9). One would have been motivated to do this because one having ordinary skill in the art would know that a slight

change in pH from 7.4 to 7.0 would not drastically affect the physical / chemical properties of the composition.

Claim Objection / Allowable Subject Matter

Claims 2,4 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Claim 12 is allowable. The prior art does teach or suggest the instant composition / solution comprising disodium phosphate or buffered at a pH of 4.5 to 5.5.

Telephonic Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alton N. Pryor whose telephone number is 703 308-4691. The examiner can normally be reached on 8:00 a.m. - 4:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page can be reached on 703-308-2927. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 308-1235.

ALTON N. PRYOR
PRIMARY EXAMINER

Alton Pryor
Patent Examiner
AU 1616

Notice of References Cited	Application/Control No. 10/129,773	Applicant(s)/Patent Under Reexamination DEARN ET AL.	
	Examiner Alton N. Pryor	Art Unit 1616	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N	WO-9802186	01-1998	WO	Penkler et al	
*	O	EP-636623	02-1995	EP	Robertson et al	
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 47/48 — A1

(11) International Publication Number: WO 98/02186

(43) International Publication Date: 22 January 1998 (22.01.98)

(21) International Application Number: PCT/GB97/01872

(22) International Filing Date: 11 July 1997 (11.07.97)

(30) Priority Data:
96/5889 11 July 1996 (11.07.96) ZA

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(54) Title: INCLUSION COMPLEX CONTAINING INDOLE SELECTIVE SEROTONIN AGONIST

(57) Abstract

An inclusion complex comprises (a) an indole selective serotonin (5-HT_{1D}) agonist or a pharmaceutically acceptable salt thereof, such as for example sumatriptan, and (b) unsubstituted or substituted beta- or gamma-cyclodextrin, such as for example methyl-beta-cyclodextrin. Pharmaceutical compositions containing the inclusion complex and the use of the inclusion complex in the treatment of migraine and cluster headaches are also disclosed.

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INCLUSION COMPLEX CONTAINING INDOLE SELECTIVE SEROTONIN AGONIST

BACKGROUND OF THE INVENTION

THIS invention relates to an inclusion complex of an indole selective serotonin (5-HT_{1D}) agonist and an unsubstituted or substituted beta- or gamma-cyclodextrin, and to pharmaceutical compositions containing such a complex, particularly for oral or nasal mucosal delivery, for the treatment of migraine or cluster headaches.

Sumatriptan (3-(2-dimethylaminoethyl)indol-5-yl-N-methylmethanesulphonamide) and other structurally related indole derivatives such as naratriptan, rizatriptan, zolmitriptan, eletriptan and almotriptan are selective serotonin (5-HT_{1D}) agonists useful for the treatment of migraine. Sumatriptan is given orally or subcutaneously as the succinate salt for the treatment of migraine. Sumatriptan is rapidly absorbed following oral administration and undergoes extensive pre-systemic metabolism,

resulting in a low bioavailability of about 14%. The bioavailability following subcutaneous administration is 96%. For the acute treatment of migraine, sumatriptan may be given in an initial dose of 100mg by mouth and a clinical response can be expected between 0,5 to 2 hours. Alternatively, sumatriptan may be given by subcutaneous injection in a single dose of 6 mg with a clinical response in 10 - 15 minutes.

Apart from the low bioavailability following oral administration of anti-migraine compounds such as sumatriptan, the classical oral route of administration has limitations in the treatment of migraine due to nausea and vomiting associated with migraine attacks. Many patients are averse to self administration by subcutaneous injection, limiting this route of administration.

The oral and nasal cavities have several advantages as sites for systemic drug delivery, particularly avoidance of presystemic metabolism. However, the low permeability of the membranes that line the oral and nasal cavities result in a low flux of drug. There is therefore a need to enhance drug penetration to improve bioavailability following oral or nasal mucosal drug delivery.

There are several methods known in the art to deliver drugs to the oral and nasal mucosae. These include buccal and sublingual tablets or lozenges, adhesive patches, gels, solutions or sprays (powder, liquid or aerosol) for the oral cavity and solutions or sprays (powder, liquid or aerosol) for the nasal cavity.

The absorption of drugs from mucosal membranes may be enhanced by (i) increasing drug solubility, (ii) pH modification to favour the unionized form of the drug, (iii) addition of mucoadhesive agents to improve contact between the delivery system and the membrane and (iv) incorporation of so-called penetration enhancers.

There are a number of penetration enhancers known to influence the permeability of drugs across epithelial membranes [for a recent review see Walker, R.B and Smith, E.W. Advanced Drug Delivery Reviews 1996, 18, 295-301].

Cyclodextrins and their derivatives have found extensive application as solubilizers and stabilizers due to their ability to form inclusion complexes with a wide variety of compounds [see (J. Szejtli, *Cyclodextrin Technology*, Kluwer Academic Press) and (J. Szejtli & K-H Fromming, *Cyclodextrins in Pharmacy*, Kluwer Academic Press)]. Cyclodextrins have been used to enhance intestinal absorption of drugs primarily through increasing solubility. Recently, cyclodextrins have been shown to have positive and negative effects on transdermal penetration of drugs [see (Loftsson, T. et al International Journal of Pharmaceutics 1995, 115, 255-258), (Vollmer, U. et al. International Journal of Pharmaceutics 1993, 99, 51-58), (Legendre, J.Y. et al. European Journal of Pharmaceutical Sciences 1995, 3, 311-322) and (Vollmer, U. et al Journal of Pharmacy and Pharmacology 1994, 46, 19-22)]. Cyclodextrins may improve nasal absorption of drugs [see (Merkus, F.W. et al. Pharmaceutical Research 1991, 8, 588-592) and (Shao, Z. et al Pharmaceutical Research 1992, 9, 1157-1163)] and enhance absorption from sublingual administration of drug/cyclodextrin complexes. Cyclodextrins also protect nasal mucosal damage by penetration enhancers [see Jabbal-Gill, I. et al. European Journal of Pharmaceutical Sciences 1994, 1(5), 229-236]

Cyclodextrins are water soluble cone-shaped cyclic oligosaccharides containing 6, 7 or 8 glucopyranose units. The interior or "cavity" of the cone is hydrophobic whilst the exterior is hydrophilic. The size of the cavity increases with increasing number of glucose units. Several cyclodextrin derivatives such as alkyl, hydroxyalkyl and sulfoalkyl ethers have been prepared with improved solubility [see (J. Szejtli & K-H Fromming, *Cyclodextrins in Pharmacy*, Kluwer Academic Press) and (Stella, V.J. et al

Pharmaceutical Research 1995, 12 (9) S205)]. Suitably sized hydrophobic "guest" molecules may enter the "host" cavity to form a classical host-guest "inclusion compound" or "inclusion complex" with either the entire guest molecule included or only a portion thereof. The driving mechanism for cyclodextrin inclusion complexation is the affinity of the hydrophobic guest molecule for the cavity of the cyclodextrin host molecule with displacement of cavity water molecules to a thermodynamically more stable state. The term "complex stability" or stability of a given inclusion complex refers to the association/dissociation equilibrium of host and guest in solution. Complex stability depends on the number of intermolecular bonding interactions between the host and guest. Van der waals forces and hydrophobic interactions are the main interactions stabilizing inclusion complexes (Bergeron, R.J. et al. *Journal of the American Chemical Society* 1977, 99, 5146). Depending on the nature and position of hydrogen bonding functionalities on a given guest, there may be hydrogen bonding between the guest and hydroxyl groups of the cyclodextrin or other hydrogen bonding groups in the case of cyclodextrin derivatives. Ionic interactions between the host and guest are also possible in the case of ionic cyclodextrins such as sulphobutyl ethers (Stella, V.J. et al Pharmaceutical Research 1995, 12 (9) S205).

Cyclodextrin inclusion complexes may be prepared on the basis of liquid state, solid state or semi-solid state reaction between the components (J. Szejtli, *Cyclodextrin Technology*, Kluwer Academic Press). The first is accomplished by dissolving the cyclodextrin and guest in a suitable solvent or mixture of solvents and subsequently isolating the solid state complex by crystallization, evaporation, spray drying or freeze drying. In the solid state method, the two components may be screened to uniform particle size and thoroughly mixed whereafter they are ground in a high energy mill with optional heating, screened and homogenized. In the semi-solid state, the two components are kneaded in the presence of small amounts of a suitable solvent, and the complex so-formed, is dried, screened and homogenized.

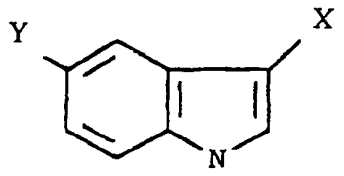
The liquid state reaction generally provides optimum conditions for completeness of reaction. Depending on solvent conditions, the dissolved inclusion complex exists in equilibrium between uncomplexed host and guest and complexed host/guest.

SUMMARY OF THE INVENTION

According to a first aspect of the invention there is provided an inclusion complex of (a) an indole selective serotonin (5-HT_{1D}) agonist or a pharmaceutically acceptable salt thereof and (b) an unsubstituted or substituted beta- or gamma- cyclodextrin.

By an indole selective serotonin (5-HT_{1D}) agonist there is meant a compound which includes the indole structure, which structure will generally be substituted, and which has selective serotonin (5-HT_{1D}) agonist activity.

The indole selective serotonin (5-HT_{1D}) agonist is preferably selected from compounds having the formula:



wherein X and Y represent suitable substitutions, more preferably from the group consisting of sumatriptan, naratriptan, rizatriptan, zolmitriptan, eletriptan and almotriptan or a pharmaceutically acceptable salt thereof. Thus, compound (a) may be used in the form of the free base or in the form of a pharmaceutically acceptable salt such as a hydrochloride, succinate, citrate, fumarate, sulphate, benzoate, or maleate salt.

The inclusion complex preferably has a stoichiometry of (a) to (b) of 1:1

mol/mol.

The inclusion complex is preferably an inclusion complex of sumatriptan free base and methyl-beta-cyclodextrin or of sumatriptan succinate and methyl-beta-cyclodextrin which has substantially the X-ray powder diffraction pattern of Figure 4 or Figure 5.

According to a second aspect of the invention there is provided a pharmaceutical composition which comprises as an active ingredient an inclusion complex of (a) an indole selective serotonin (5-HT_{1D}) agonist or a pharmaceutically acceptable salt thereof and (b) an unsubstituted or substituted beta- or gamma-cyclodextrin.

The pharmaceutical composition is preferably for use in the treatment of migraine and cluster headaches.

The pharmaceutical composition is preferably adapted for oral or nasal mucosal delivery.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention will now be described in more detail, by way of example only, with reference to the accompanying drawings in which:

Figure 1 shows a differential scanning calorimetry thermogram of sumatriptan succinate with the onset melting temperature of 166°C and sharp endothermic melting peak at 167,9°C;

Figure 2 shows a differential scanning calorimetry thermogram of a 1:1 kneaded complex of sumatriptan succinate and methyl-beta-cyclodextrin obtained from Example 1;

Figure 3 shows a differential scanning calorimetry thermogram of a 1:1 kneaded complex of sumatriptan succinate and methyl-beta-cyclodextrin containing 1 molar equivalent of tromethamine obtained from Example 2;

Figure 4 shows an X-ray powder diffraction pattern of the 1:1 kneaded complex of sumatriptan succinate and methyl-beta-cyclodextrin obtained from Example 1;

Figure 5 shows an X-ray powder diffraction pattern of the 1:1 kneaded complex of sumatriptan succinate and methyl-beta-cyclodextrin containing one molar equivalent of tromethamine obtained from Example 2; and

Figure 6 shows a cut-away perspective of the geometry optimized molecular mechanical model of an inclusion complex of sumatriptan (pale grey) in beta-cyclodextrin (dark grey).

DESCRIPTION OF EMBODIMENTS

The crux of the invention is an inclusion complex of (a) an indole selective serotonin ($5\text{-}HT_{1D}$) agonist or a pharmaceutically acceptable salt thereof and (b) an unsubstituted or substituted beta- or gamma-cyclodextrin.

Examples of suitable compounds (a) are sumatriptan, naratriptan, rizatriptan, zolmitriptan, eletriptan and almotriptan. The compound may be used in the form of the free base or in the form of a pharmaceutically acceptable salt such as a hydrochloride, succinate, citrate, fumarate, sulphate, benzoate, or maleate salt or the like.

The second component of the inclusion complex is an unsubstituted or

substituted beta- or gamma-cyclodextrin.

Highly water soluble cyclodextrins such as 2-hydroxypropylated or methylated or sulphoalkylated derivatives of beta-cyclodextrin are the preferred cyclodextrins of the invention. Gamma-cyclodextrin or 2-hydroxypropylated or methylated or sulphoalkylated derivatives of gamma-cyclodextrin may also be used in the same manner as the corresponding preferred beta-cyclodextrin derivatives. The degree of substitution of the cyclodextrin derivatives may vary between 1 to 20 substituents per cyclodextrin molecule but more preferably between 3 to 15 substituents per cyclodextrin molecule. When the cyclodextrin is 2-hydroxypropyl-beta-cyclodextrin, the preferred degree of substitution is between 3.9 and 5.1 hydroxypropyl groups per cyclodextrin molecule. When the cyclodextrin is methyl-beta-cyclodextrin, the preferred degree of substitution is between 1.8 and 2 methyl groups per glucose unit.

The inclusion complex of the invention may be prepared from aqueous solutions, slurries or pastes of the indole derivative and cyclodextrin according to conventional methods. The molar ratio of indole derivative to cyclodextrin may vary between 1:1 to 1:10 but more preferably between 1:1 to 1:5. Solutions are prepared by dissolving the cyclodextrin in a sufficient quantity of purified deionised water which may be optionally buffered between pH 7.4 to 8.5. The indole derivative is added to the solution with stirring until dissolved. The solution may be used in the preparation of liquid delivery systems such as drops, sprays or aerosols. Where a solid inclusion complex is desired, the solution or slurry may be dried by spray drying or freeze drying.

Alternatively, the indole derivative and cyclodextrin are mixed. The powder mixture is wetted with water, optionally containing a buffer pH 7.4 - 8.5, while mixing vigorously until a paste is formed. The paste is mixed for 0.25 to 2 hours and dried in an oven or in vacuo at elevated temperature. The

dried complex is crushed and sieved to the desired particle size.

A pharmaceutically acceptable buffer, capable of buffering in the pH range 7.4 - 8.5 may be used in the formation of the inclusion complex, particularly when the indole derivative is present as a salt. Preferred buffers include tromethamine, triethanolamine, diethanolamine, phosphate buffer, sodium bicarbonate, and sodium carbonate. The concentration of the buffer may vary from 0.5 to 5 molar equivalents relative to the indole.

The second aspect of the invention is a pharmaceutical composition which comprises as an active ingredient an inclusion complex as described above.

The pharmaceutical composition of the invention is of particular application in the treatment of migraine and cluster headaches.

Further, the pharmaceutical composition of the invention is preferably adapted for oral or nasal mucosal delivery.

The administration of an anti-migraine drug through the mucosal tissue of the nose or mouth avoids the problems associated with administration of indole serotonin agonists by injection (i.e. patient aversion and painful administration) and oral administration (i.e. slow onset of action, low bio-availability and poor compliance due to nausea and vomiting associated with migraines).

Absorption of the drug from the pharmaceutical composition of the invention is rapid such that the drug reaches the systemic circulation almost as fast as through injection and appreciably faster than oral administration, which is highly advantageous for the rapid relief of migraine attack or cluster headache.

Further, the unpleasant taste and irritant properties of the active principle are

reduced by presenting the drug to the nasal or oral mucosal membranes in the form of a cyclodextrin inclusion complex.

The present invention achieves these advantages by molecular encapsulation of the anti-migraine indole drug in a cyclodextrin, so forming a molecular inclusion complex which may be used in the solid form for the preparation of sublingual or buccal tablets, buccal patches or nasal inhalation powders (insufflations). The inclusion complex may be used in the liquid state for the preparation of metered dose sprays, drops or pressurized aerosols for nasal or oral administration. The complex according to the invention may be incorporated into a shearform matrix designed for immediate release as described in Fuisz Technologies Ltd patents (Eur. Pat. Appl. EP 95-650038 and PCT Int. Appl. WO 95/34293).

According to the invention, the indole nucleus of selective serotonin (5-HT_{1D}) agonists has been found to be readily included in the cavity of beta-cyclodextrins such as hydroxypropyl-beta-cyclodextrin and methyl-beta-cyclodextrin to form molecular inclusion complexes with a 1:1 mol/mol stoichiometry. Inclusion complexes of a variety of indole-based serotonin agonists may therefore be prepared according to methods known in the art such as spray drying, freeze drying and kneading, as described above. The complexes according to the invention may also be incorporated into microspheres by methods appreciated in the art. The complexes according to the invention are stable, amorphous and highly water soluble.

Penetration enhancers may be used to promote the passage of the indole derivative across the mucosal membranes. Typical permeation enhancers include fatty acids and their salts such as sodium caprate, sodium caprylate and sodium oleate, sodium laurate, and bile salts such as sodium glycodeoxycholate, sodium glycocholate, sodium cholate and sodium taurodeoxycholate. Other penetration enhancers may include tensides, ionic surfactants such as sodium lauryl sulphate, or non-ionic surfactants such as

polyethylene glycol 660 hydroxystearate or polyoxyethylene lauryl ethers, fusidates such as sodium taurodihydrofusidate. Other specific enhancers include azone and chitosan. Combinations of permeation enhancers such as polyoxyethylene 8 lauryl ether and sodium glycocholate or mixed micelles such as sodium caprate and sodium glycocholate may also be used. The penetration enhancers may also be used in combination with beta or gamma-cyclodextrins or their methyl, hydroxypropyl or sulphoalkyl derivatives. Typical concentrations of permeation enhancers are between 0,1 % to 5%, more preferably between 0,25% to 3% by weight of the composition.

As stated above, the serotonin (5-HT_{1D}) agonist may be used in the form of the free base or a pharmaceutically acceptable salt. When acidic penetration enhancing excipients are used such as bile acids or fatty acids or pharmaceutically acceptable salts of bile acids or fatty acids, salt formation between the basic component of the serotonin (5-HT_{1D}) agonists and the acidic component of the bile or fatty acid may occur.

Buffering agents may be incorporated into the pharmaceutical composition of the invention to control the microenvironmental pH surrounding the drug delivery system in the alkaline range, so as to maximize the percentage of the unionized form of the drug. Drugs in the unionized form cross mucosal membranes more readily than the corresponding unionized form.

Liquid compositions suitable for nasal or oral administration may contain a suitable quantity of viscosity modifying agents such as hypromellose or carbopol 934P and preservative agents such as chlorhexidine gluconate or thiomersal.

Oral compositions may contain suitable flavouring and sweetening agents such as cherry, mint, spearmint, vanilla, aspartame, sucrose, xylitol, saccharin and the like.

Typical sublingual or buccal tablets may include lubricants such as magnesium stearate, calcium stearate and sodium stearyl fumarate to facilitate tablet compression, diluents such as lactose, microcrystalline cellulose, maize starch and the like and mucoadhesive agents such as chitosan, carbopol 934P, and hydroxypropylcellulose and the like.

Typical disintegrants to enhance sublingual tablet disintegration may include sodium carboxymethylcellulose, sodium starch glycolate, polyplasdone XL, and dried starch.

The following examples illustrate the present invention.

EXAMPLE 1

Sumatriptan succinate (1g) and methyl-beta-cyclodextrin (3,18) are mixed in a mortar. Purified deionised water (2ml) is added in aliquots with mixing to form a uniform paste. Mixing is continued for 0.5 hours and the paste is transferred to a vacuum oven and dried at 40°C and 5 millibar. The dried complex is crushed with a pestle and passed through a 60 mesh (250 micron) sieve. The complex contains 23,0 % m/m (mass/mass) sumatriptan succinate as determined by HPLC.

EXAMPLE 2

Tromethamine (0,293g) was dissolved in 5 ml purified deionised water. Sumatriptan succinate (1g) and methyl-beta-cyclodextrin (3,18g) are mixed in a mortar. The tromethamine solution is added in aliquots with mixing to form a uniform paste. Mixing is continued for 0,5 hours and the paste is transferred to a vacuum oven and dried at 40°C and 5 millibar. The dried complex is crushed with a pestle and passed through a 60 mesh (250 micron) sieve. The complex contains 21,7 % m/m sumatriptan succinate as determined by HPLC.

EXAMPLE 3

The unit composition of a sublingual tablet containing the equivalent of 20 mg sumatriptan base is as follows:

Sumatriptan/methyl-beta-cyclodextrin complex (from Example 2)	130mg
Lactose NF	20mg
Magnesium stearate	1mg

The complex is blended with the lactose. The lubricant is screened in and the mixture is blended and formed into sublingual tablets by compression at 10 - 30N.

EXAMPLE 4

The unit composition of a sublingual tablet containing the equivalent of 20 mg sumatriptan base is as follows:

Sumatriptan/methyl-beta-cyclodextrin complex (from Example 1)	122mg
Xylitol	28mg
Sodium caprate	3.75mg
Magnesium stearate	1mg

The complex is blended with the xylitol and sodium caprate. The lubricant is screened in and the mixture is blended and formed into sublingual tablets by compression at 10 - 30N.

EXAMPLE 5

Hydroxypropyl-beta-cyclodextrin (3,39g) is dissolved in purified deionised water (8ml) buffered to pH 7,4 with phosphate buffer. Sumatriptan succinate (1g) is added to the solution with stirring. The solution is stirred for 20

minutes and then sodium caprate (25mg) and chlorhexidine gluconate (0,01%) is added. The volume is adjusted to 10 ml by addition of phosphate buffer pH 7,4 and the tonicity of the final solution is adjusted with sodium chloride to 300 mOsm/kg. The solution is filtered and filled into a metered dose nasal spray bottle. Each 0,1 ml metered dose contains 10 mg sumatriptan succinate suitable for nasal administration.

Referring now to the drawings, Figure 1 shows a differential scanning calorimetry thermogram of sumatriptan succinate with the onset melting temperature of 166°C and sharp endothermic melting peak at 167,9°C. The thermogram was recorded on a Perkin-Elmer DSC7 calorimeter with a heating rate of 5°C per minute. A sample mass of 1.36 mg was used.

Figure 2 shows a differential scanning calorimetry thermogram of a 1:1 kneaded complex of sumatriptan succinate and methyl-beta-cyclodextrin obtained from Example 1. The characteristic melting endotherm of sumatriptan succinate shown in Figure 1 is absent, providing evidence of inclusion complexation between sumatriptan and methyl-beta-cyclodextrin. Characteristic decomposition of methyl-beta-cyclodextrin is seen from 175°C. Experimental conditions where as described in Example 1, except that a sample mass of 11,1 mg was used to provide a sumatriptan succinate response equivalent to Example 1.

Figure 3 shows a differential scanning calorimetry thermogram of a 1:1 kneaded complex of sumatriptan succinate and methyl-beta-cyclodextrin containing 1 molar equivalent of tromethamine obtained from Example 2. The characteristic melting endothermy of sumatriptan succinate shown in Figure 1 is absent. An endotherm corresponding to the free base at 89°C is also absent providing evidence of inclusion complexation between sumatriptan and methyl-beta-cyclodextrin. Characteristic decomposition of methyl-beta-cyclodextrin is seen from 175°C. Experimental conditions were as described in Example 1 except that a sample mass of 12,42 mg was used

to provide a sumatriptan succinate response equivalent to Example 1.

Figure 4 shows an X-ray powder diffraction pattern of the 1:1 kneaded complex of sumatriptan succinate and methyl-beta-cyclodextrin obtained from Example 1. The absence of resolved sharp peaks characteristic of crystalline sumatriptan succinate indicates inclusion complexation with resultant loss of crystallinity. The resulting diffraction pattern is characteristic of an amorphous solid.

Figure 5 shows an X-ray powder diffraction pattern of the 1:1 kneaded complex of sumatriptan succinate and methyl-beta-cyclodextrin containing 1 molar equivalent of tromethamine obtained from Example 2. The absence of resolved sharp peaks characteristic of crystalline sumatriptan succinate and tromethamine indicates inclusion complexation with resultant loss of crystallinity. The resulting diffraction pattern is characteristic of an amorphous solid.

Figure 6 shows a cut-away perspective of the geometry optimised molecular mechanical model of an inclusion complex of sumatriptan (pale grey) in beta-cyclodextrin (dark grey). The indole nucleus fills the cavity with the pendant dimethylaminoethyl (bottom) and methanesulphonamide (top) side chains extending out of the cavity.

CLAIMS

1 An inclusion complex of (a) an indole selective serotonin ($5\text{-}HT_{1D}$) agonist or a pharmaceutically acceptable salt thereof and (b) an unsubstituted or substituted beta-or gamma-cyclodextrin.

2 An inclusion complex according to claim 1 wherein (a) is sumatriptan or a pharmaceutically acceptable salt thereof.

3 An inclusion complex according to claim 1 wherein (a) is selected from the group consisting of naratriptan, rizatriptan, zolmitriptan, eletriptan and almotriptan and the pharmaceutically acceptable salts thereof.

4 An inclusion complex according to any one of claims 1 to 3 wherein (b) is selected from the group consisting of 2-hydroxypropyl-beta-cyclodextrin, a methylated-beta-cyclodextrin, and a sulphoalkylated beta-cyclodextrin.

5 An inclusion complex according to any one of claims 1 to 4 wherein (b) has a degree of substitution between 1 to 20 substituents per cyclodextrin molecule.

6 An inclusion complex according to claim 5 wherein (b) has a degree of substitution between 3 to 15 substituents per cyclodextrin molecule.

7 An inclusion complex according to any one of claims 1 to 3 wherein (b) is 2-hydroxypropyl beta-cyclodextrin with a degree of substitution between 3,9 and 5,1 hydroxypropyl groups per cyclodextrin molecule.

8 An inclusion complex according to any one of claims 1 to 3 where (b) is methyl-beta-cyclodextrin with a degree of substitution between 1.8 and 2 methyl groups per glucose unit.

9 An inclusion complex of sumatriptan free base and methyl-beta-cyclodextrin.

10 An inclusion complex of sumatriptan succinate and methyl-beta-cyclodextrin.

11 An inclusion complex of sumatriptan succinate and methyl-beta-cyclodextrin having substantially the X-ray powder diffraction pattern of Figure 4 or Figure 5.

12 An inclusion complex according to any one of claims 1 to 11 wherein the inclusion complex has a stoichiometry of (a) to (b) of 1:1 mol/mol.

13 A pharmaceutical composition comprises as an active ingredient an inclusion complex of (a) an indole selective serotonin ($5\text{-}HT_{1D}$) agonist or a pharmaceutically acceptable salt thereof and (b) an unsubstituted or substituted beta- or gamma-cyclodextrin.

14 A pharmaceutical composition according to claim 13 wherein the inclusion complex is as defined in any one of claims 2 to 12.

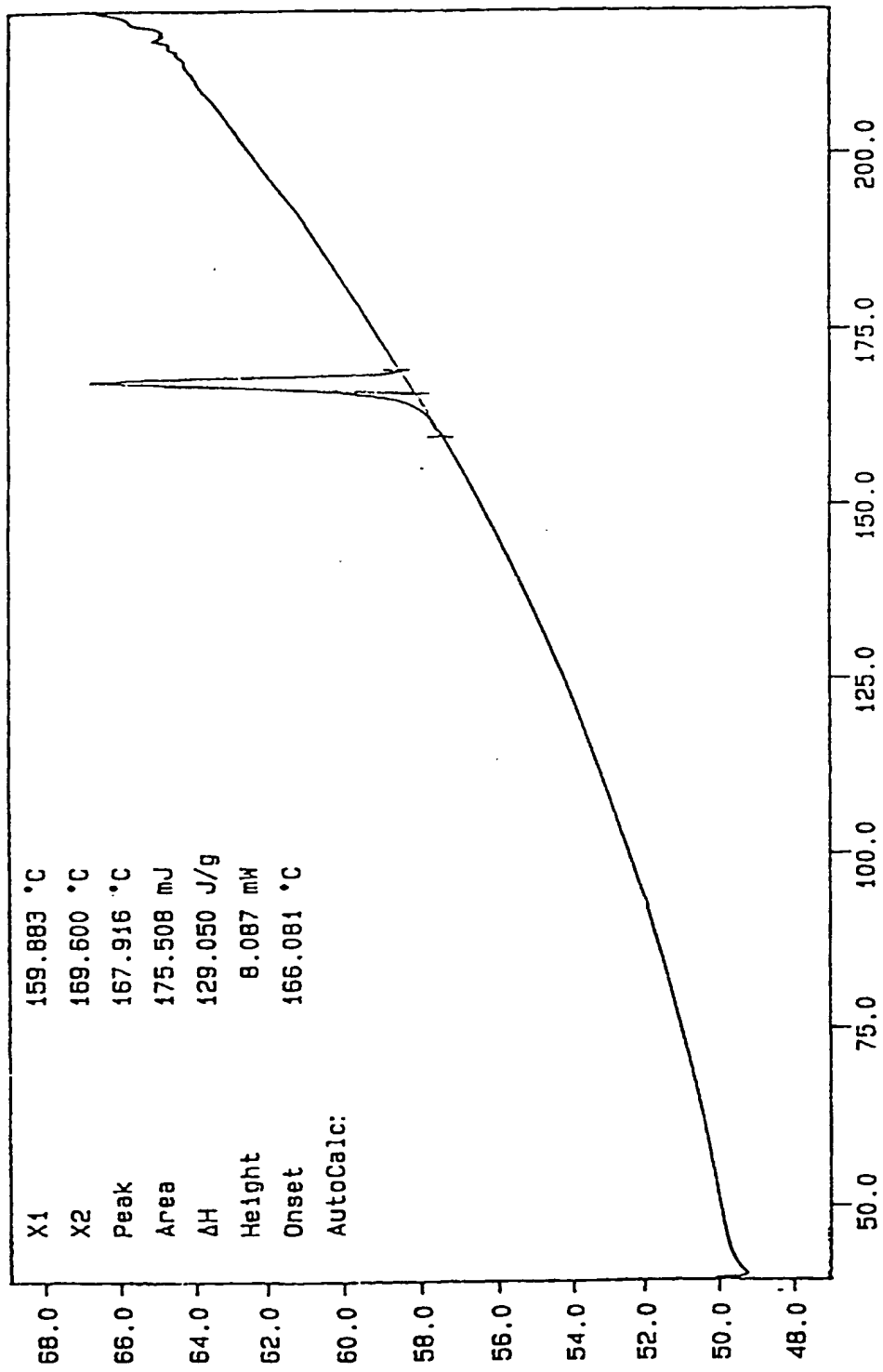
15 A pharmaceutical composition according to claim 13 or claim 14 for use in the treatment of migraine or cluster headaches.

16 A pharmaceutical composition according to any one of claims 13 to 15 formulated for oral or nasal mucosal delivery.

17 The use of an inclusion complex of (a) an indole selective serotonin ($5\text{-}HT_{1D}$) agonist or a pharmaceutically acceptable salt thereof and (b) an unsubstituted or substituted beta- or gamma-cyclodextrin in the manufacture of a medicament for use in the treatment of migraine or cluster headaches.

18 The use according to claim 17 wherein the inclusion complex is as defined in any one of claims 2 to 12.

FIGURE 1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X2 169.600 °C
Peak 167.916 °C
Area 175.508 mJ
ΔH 129.050 J/g
Height 8.087 mW
Onset 166.081 °C
AutoCalc:
68.0
66.0
64.0
62.0
60.0
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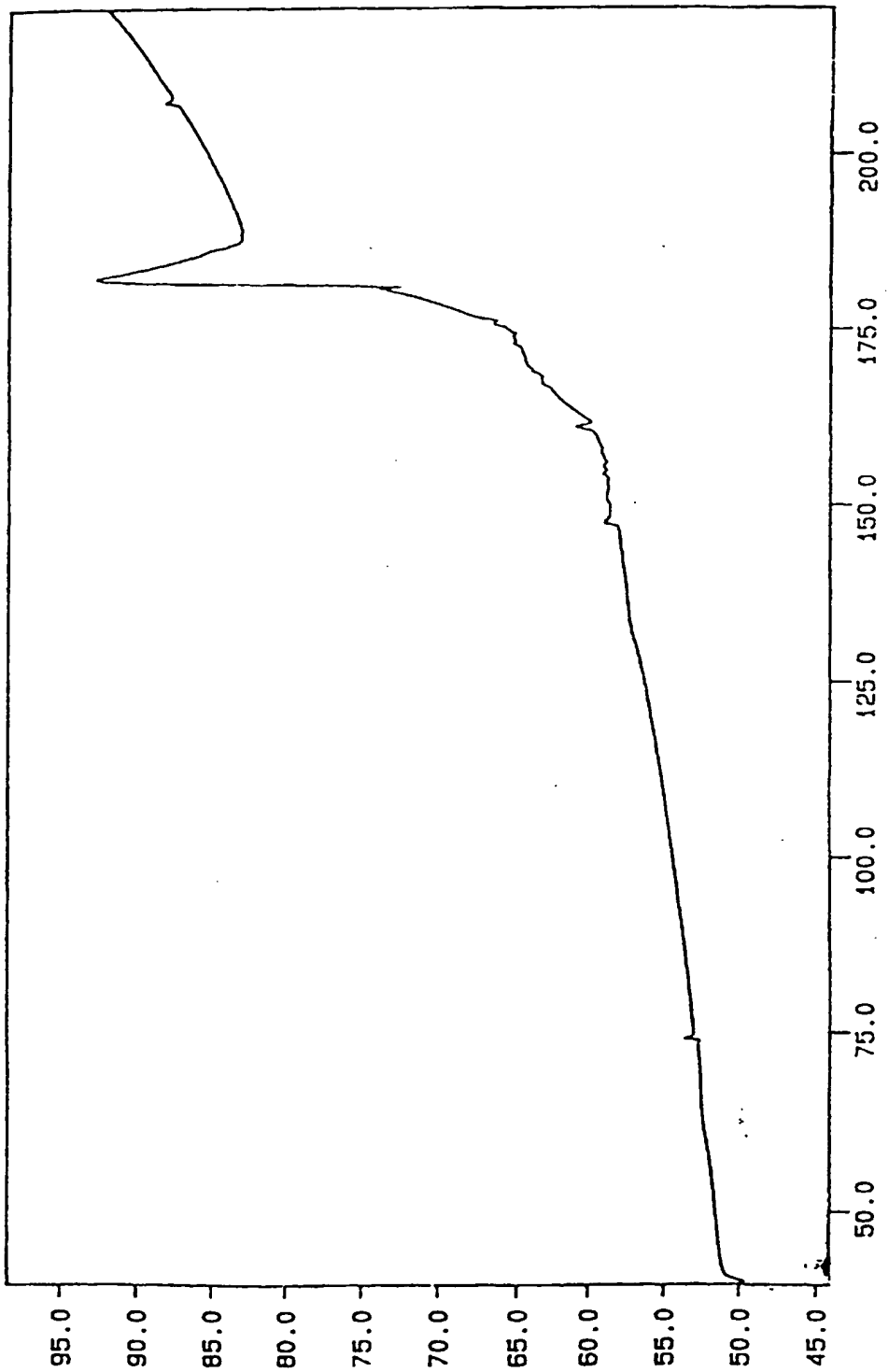
75.0
100.0
125.0
150.0
175.0
200.0

FIGURE 2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85.0
80.0
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70.0
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45.0
50.0
75.0
100.0
125.0
150.0
175.0
200.0

FIGURE 3

Heat Flow (mW)

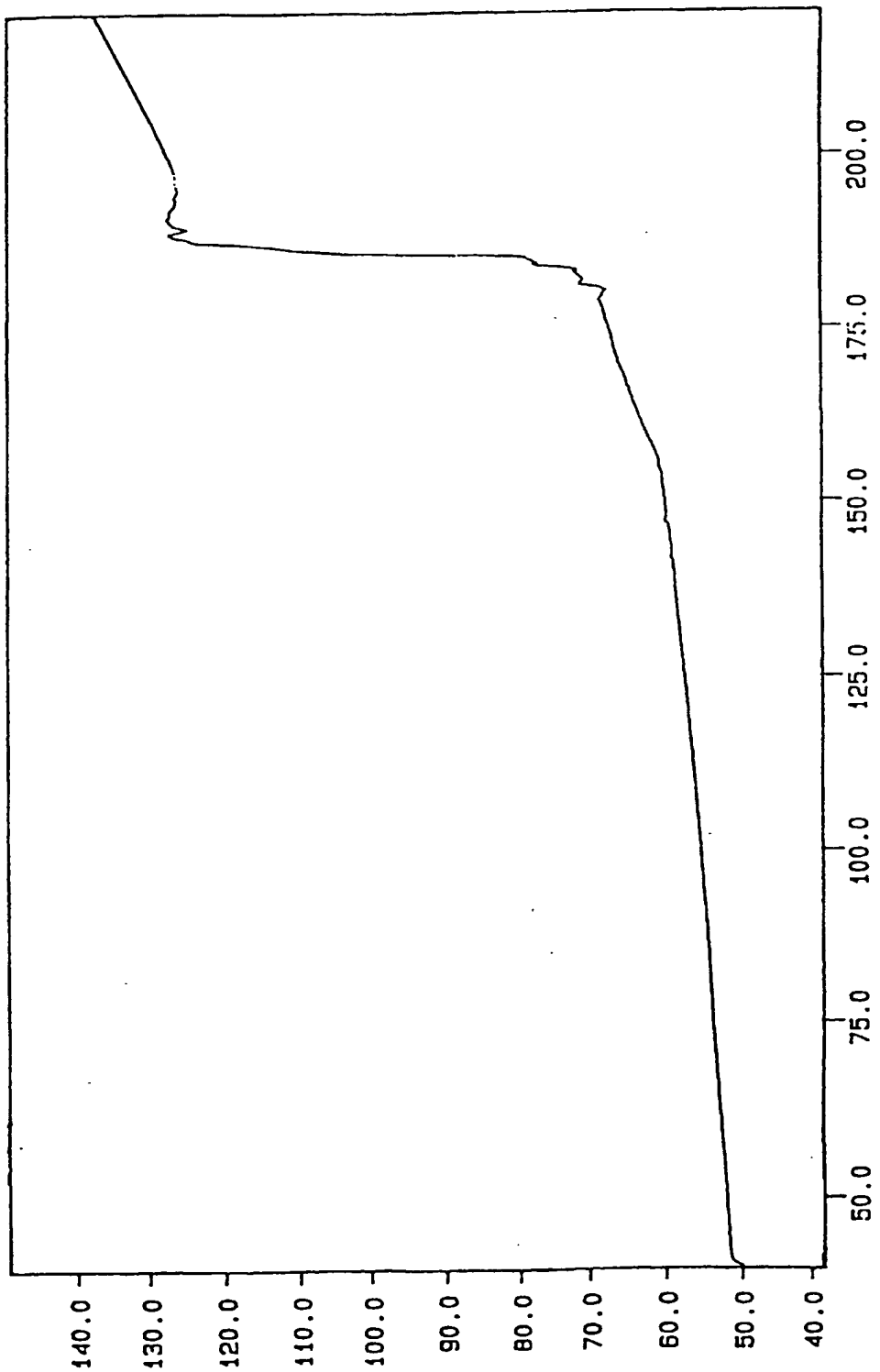
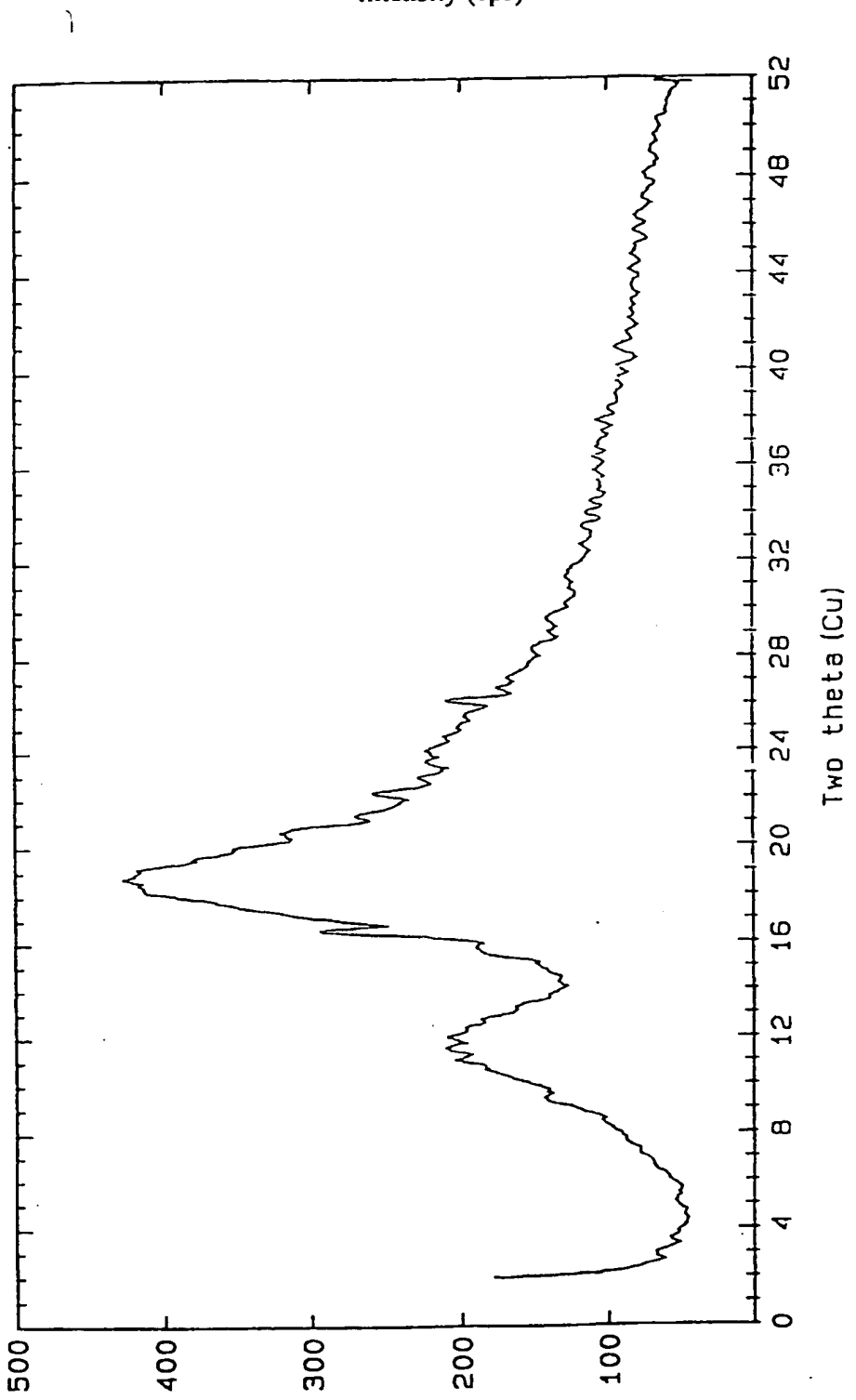


FIGURE 4


Intensity (cps)
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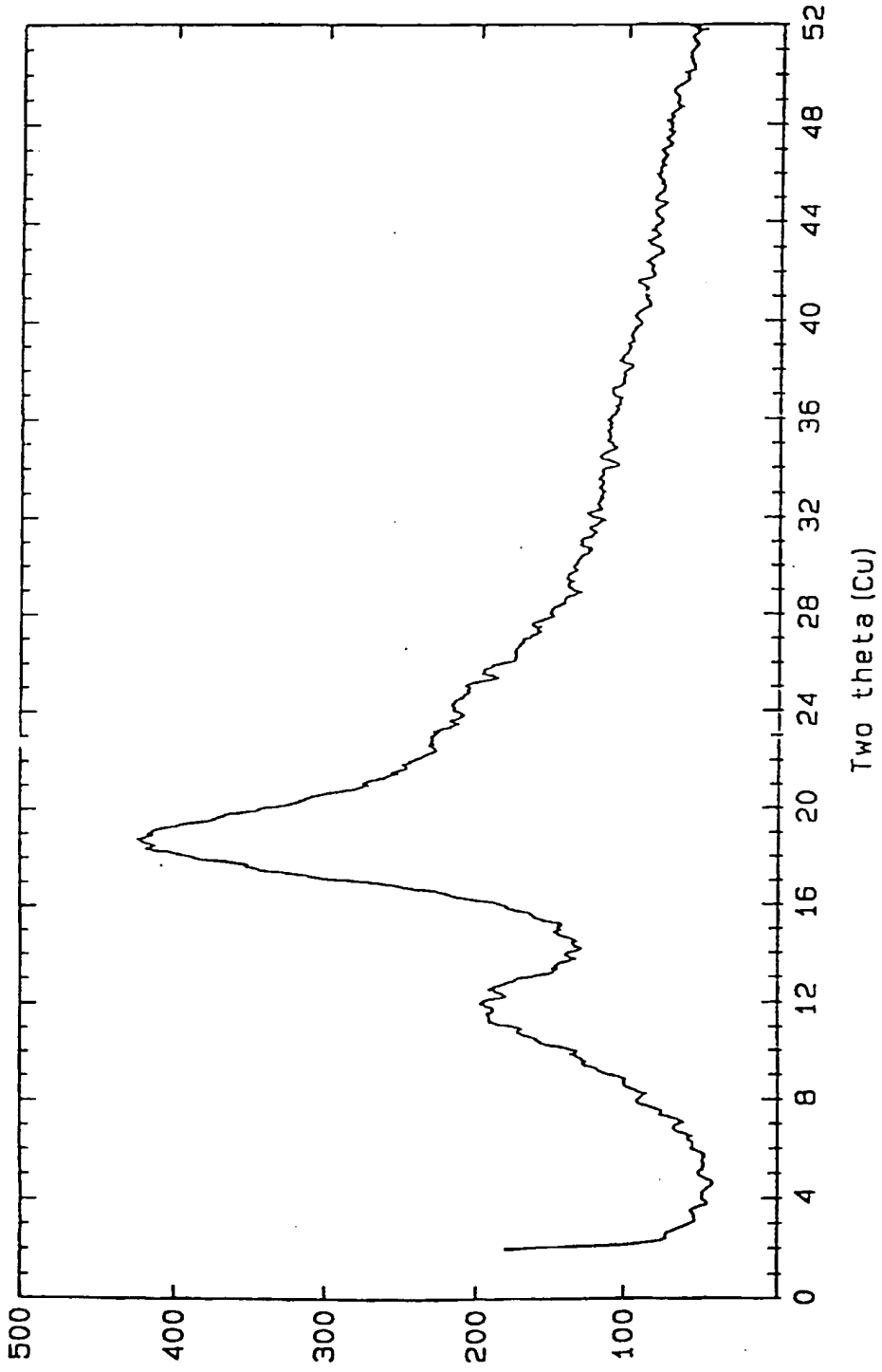
52
Two theta (Cu)

FIGURE 5


Intensity (cps)
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48
52
Two theta (Cu)

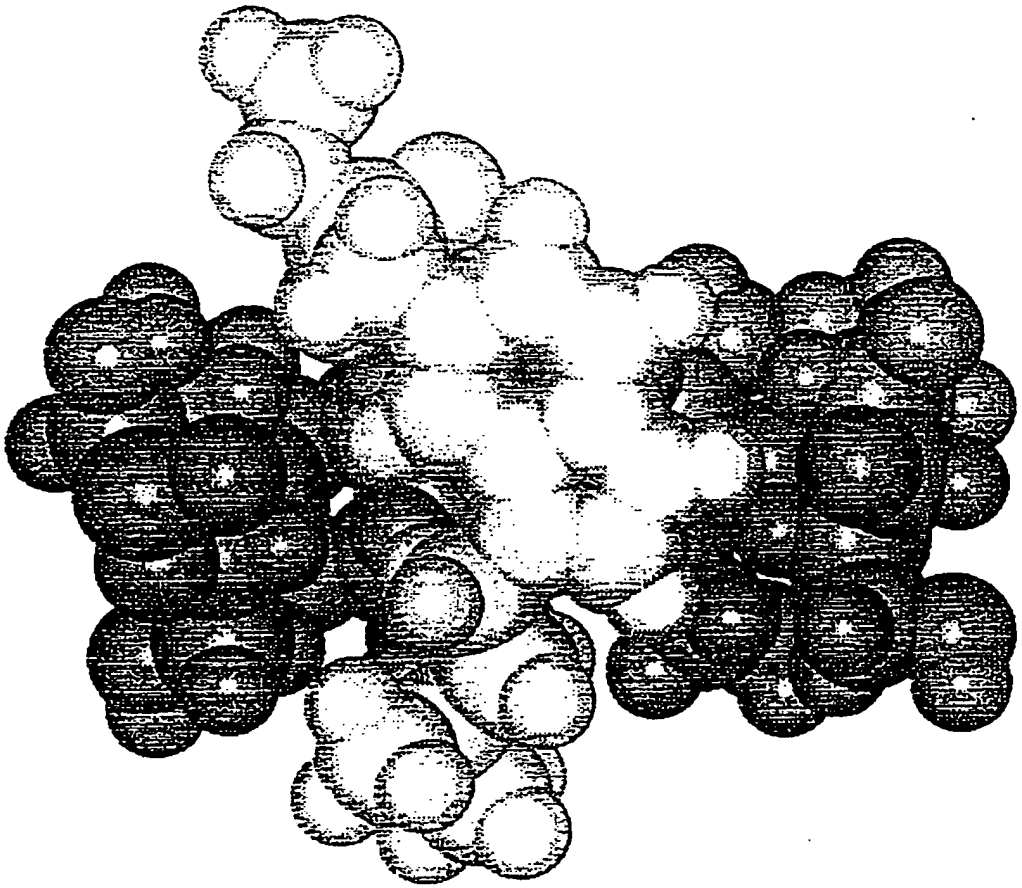

FIGURE 6

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 97/01872

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K47/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EVANS, ROGER G. ET AL: "Effects of 5-HT-receptor and.alpha.2-adrenoceptor ligands on the hemodynamic response to acute central hypovolemia in conscious rabbits" BR. J. PHARMACOL. (1993), 109(1), 37-47 CODEN: BJPCBM;ISSN: 0007-1188, 1993, XP002047442 see page 38, column 1, paragraph 3 ---	1-18
A	US 5 288 498 A (STANLEY THEODORE H ET AL) 22 February 1994 see claims 1,154,191 ---	1-18
A	US 5 288 497 A (STANLEY THEODORE H ET AL) 22 February 1994 see claims 1,167,203 ------	1-18

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 November 1997	11/12/1997

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Berte, M

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 97/01872

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5288498 A	22-02-94	CA 1338978 A	11-03-97
		US 4671953 A	09-06-87
		AT 138562 T	15-06-96
		AU 642664 B	28-10-93
		AU 6337190 A	08-04-91
		DE 69027216 D	04-07-96
		DE 69027216 T	17-10-96
		EP 0490944 A	24-06-92
		ES 2089027 T	01-10-96
		JP 5500058 T	14-01-93
		WO 9103236 A	21-03-91
		AT 116131 T	15-01-95
		CA 1271421 A	10-07-90
		CA 1339190 A	29-07-97
		DE 3650189 D	09-02-95
		DE 3650189 T	04-05-95
		EP 0200490 A	05-11-86
		EP 0487520 A	03-06-92
		EP 0490891 A	24-06-92
		EP 0404205 A	27-12-90
		US 4863737 A	05-09-89
		US 4885173 A	05-12-89
		WO 9103099 A	07-03-91
		WO 9103234 A	21-03-91
		US 5484602 A	16-01-96
		US 5132114 A	21-07-92
		US 5122127 A	16-06-92
		US 5288497 A	22-02-94
US 5288497 A	22-02-94	CA 1338978 A	11-03-97
		US 4671953 A	09-06-87
		AT 129148 T	15-11-95
		AU 668004 B	18-04-96
		AU 5521894 A	28-04-94
		AU 645265 B	13-01-94
		AU 6287790 A	08-04-91
		DE 69023143 D	23-11-95
		DE 69023143 T	28-03-96
		EP 0490916 A	24-06-92
		EP 0630647 A	28-12-94

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 97/01872

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5288497 A		ES 2077686 T	01-12-95
		JP 5503917 T	24-06-93
		WO 9103237 A	21-03-91
		AT 116131 T	15-01-95
		CA 1271421 A	10-07-90
		CA 1339190 A	29-07-97
		DE 3650189 D	09-02-95
		DE 3650189 T	04-05-95
		EP 0200490 A	05-11-86
		EP 0487520 A	03-06-92
		EP 0490891 A	24-06-92
		EP 0404205 A	27-12-90
		US 4863737 A	05-09-89
		US 4885173 A	05-12-89
		WO 9103099 A	07-03-91
		WO 9103234 A	21-03-91
		US 5484602 A	16-01-96
		US 5132114 A	21-07-92
		US 5122127 A	16-06-92
		US 5288498 A	22-02-94

PTO/SB/08A (10-01)
Approved for use through 10/31/2002.OMB 0651-0031
U. S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	Not Yet Assigned
Filing Date	May 9, 2002
First Named Inventor	Alan R. Dearn
Art Unit	N/A
Examiner Name	Not Yet Assigned
Attorney Docket Number	ASZD-P01-617

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
	BA	EP 0 636 623 A1	02-01-1995			
	BB	WO 98/02187	01-22-1998			
	BC	WO 98/34595	08-13-1998			
	BD	GB 2 315 673 A	02-11-1998			

[1] Applicant's unique citation designation number (optional). [2] See attached Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the application number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

OTHER PRIOR ART – NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]

Examiner Signature		Date Considered	8/22/03

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

[1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached.

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Term	Documents
(1 NOT 3).DWPI.	6
(L1 NOT L3).DWPI.	6

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US Pre-Grant Publication Full-Text Database
JPO Abstracts Database
EPO Abstracts Database
Derwent World Patents Index
IBM Technical Disclosure Bulletins

Search: L5

Refine Search

Recall Text | Clear

Search History

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DB=DWPI; PLUR=YES; OP=ADJ			
L5	l1 not l3	6	L5
L4	citr$7	35628	L4
L3	l1 and L2	5	L3
L2	ph	261979	L2
L1	zolmitriptan or zomig or bw311c90 or bw 311c90	11	L1

END OF SEARCH HISTORY

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FILE 'REGISTRY' ENTERED AT 17:41:19 ON 21 AUG 2003

L1 STRUCTURE UPLOADED

L2 QUE L1

L3 0 S L1

L4 0 S L1 FULL

WEST

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Search Results - Record(s) 1 through 6 of 6 returned.

☐ 1. Document ID: US 20030005925 A1

L5: Entry 1 of 6 File: DWPI Jan 9, 2003

DERWENT-ACC-NO: 2003-341273
DERWENT-WEEK: 200342

TITLE: Aerosol useful in the treatment of e.g. migraine by inhalation therapy contains particles comprising rizatriptan or zolmitriptan

INVENTOR: HALE, R L; RABINOWITZ, J D ; SOLAS, D W ; ZAFFARONI, A C

PRIORITY-DATA: 2002US-0155621 (May 22, 2002), 2001US-294203P (May 24, 2001), 2001US-317479P (September 5, 2001), 2001US-336218P (October 30, 2001), 2001US-332280P (November 21, 2001)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
US 20030005925 A1	January 9, 2003		011	A61M011/00

INT-CL (IPC): A61 M 11/00; A61 M 16/10

ABSTRACTED-PUB-NO: US20030005925A
BASIC-ABSTRACT:

NOVELTY - An aerosol for inhalation therapy contains particles comprising at least 10 (preferably 90, especially 97) wt.% of rizatriptan (I) or zolmitriptan (II).

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a kit for delivering (I) or (II) comprising a composition containing at least 5 (preferably 10) wt.% of (I) or (II) and a device comprising:

(1) an element for heating the composition to form a vapor;

(2) an element allowing the vapor to cool to form a condensation aerosol; and

(3) an element permitting the mammal to inhale the aerosol.

ACTIVITY - Antimigraine; Analgesic.

MECHANISM OF ACTION - 5-HT1-Receptor-Agonist.

USE - To deliver rizatriptan or zolmitriptan to a mammal through an inhalation route (claimed) as active ingredient in anti-migraine composition; for the treatment of headache including cluster headache, chronic paroxysmal hemicrania, headache associated with vascular disorder, tension headache and pediatric migraine.

ADVANTAGE - The compounds rizatriptan and zolmitriptan exhibit vasoconstrictor activity and the inhalation route of these compounds for the treatment of headache, rapidly produces their peak plasma concentrations.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw. Desc | Image

☐ 2. Document ID: EP 1290220 A1 WO 200179554 A1

L5: Entry 2 of 6 File: DWPI Mar 12, 2003

DERWENT-ACC-NO: 2002-034367
DERWENT-WEEK: 200320

TITLE: Determining predisposition for QT interval prolongation when treated with pharmaceutical agents by identifying genetic polymorphisms or mutations located in long QT, altered sensitivity or increased exposure genes

INVENTOR: WOOSLEY, R L

PRIORITY-DATA: 2000US-196916P (April 13, 2000)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
EP 1290220 A1	March 12, 2003	E	000	C12Q001/68
WO 200179554 A1	October 25, 2001	E	077	C12Q001/68

INT-CL (IPC): C07 H 21/04; C12 Q 1/68

ABSTRACTED-PUB-NO: WO 200179554A
BASIC-ABSTRACT:

NOVELTY - Determining (I) whether a subject has predisposition for QT interval elongation when treated with one or more pharmaceutical agents, comprising screening a biological sample from the subject through a nucleic acid array containing probes for one or at least two genetic mutations or polymorphisms in at least two genes, chosen from long QT (LQT), altered sensitivity or increased exposure genes, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a nucleic acid array comprising nucleic acids which recognize and bind to at least two gene mutations and/or polymorphisms located in genes found in at least two classes of genes chosen from LQT, AS and IE genes;

(2) a nucleic acid array which is capable of screening the 22 alleles of the cytochrome P450 enzyme (CYP2D6) gene and further comprising a nucleic acid which recognizes and binds to at least one ion channel gene mutation;

(3) screening (II) a pharmaceutical agent in vitro for its ability to induce prolonged cardiac repolarization in a cell, comprising:

(i) measuring IKr (rapid component of the delayed rectifier potassium current) and IKs (slower component of the delayed rectifier current) currents of the cell using a voltage clamp;

(ii) superfusing and incubating the cell with the candidate agent(s);

(iii) measuring the IKr and IKs currents after superfusion and incubation of the cell with the candidate agent(s) using a voltage clamp; and

(iv) determining whether both the IKr or the IKs current is inhibited or abolished, which indicates that the drug prolongs repolarization;

(4) screening two or more pharmaceutical agents in vitro for their ability to induce cardiac arrhythmias associated with QT interval prolongation, comprising:

(i) measuring IKr and IKs currents as above with two or more pharmaceutical agents;

(ii) superfusing and incubating the cell with the two or more pharmaceutical agents;

(iii) measuring the IKr and IKs currents after superfusing and incubation of the cell with the two or more agents using a voltage clamp;

(iv) comparing the IKr and IKs currents of the combined pharmaceutical agents on the cell with the IKr and IKs currents of each of the pharmaceutical agents alone in the cell; and

(v) determining whether IKr and IKs currents are both inhibited such that beating of the cells is substantially inhibited; and

(5) identifying (III) a genetic polymorphism which can cause QT interval prolongation in a subject, comprising:

(i) inserting a nucleic acid(s) into a cell which encode two polymorphisms and/or mutations of LQT, AS and IE genes;

(ii) measuring IKs and IKr currents of the cell before administering a drug known to cause a change in IKs and/or IKr;

(iii) measuring IKs and IKr currents of the cell after superfusion of the cell with the drug;

(iv) comparing the IKs and IKr values of the cell expressing the polymorphisms and/or mutations to the IKs and IKr value of a cell expressing wild-type genes; and

(v) determining if the presence of the mutations and/or polymorphisms leads to greater inhibition or blockage of IKs and/or IKr.

USE - (I) is useful for determining whether a subject has a predisposition for QT interval prolongation when treated with one or more pharmaceutical agents such as amiodarone, amitriptyline, amoxapine, astemizole, azelastine, bepridil, chlorpromazine, cisapride, clarithromycin, clemastine, clomipramine, desipramine, diphenhydramine, disopyramide, doxepin, erythromycin, felbamate, flecainide, fluconazole, fludrocortisone, fluoxetine, fluphenazine, fluvoxamine, foscarnet, fosphenytoin, halofantrine, haloperidol, ibutilide, imipramine, indapamide, ipecac, isradipine, itraconazole, ketoconazole, levomethadyl, maprotiline, moexipril/HCTZ, moricizine, naratriptan, nicardipine, nortriptyline, octreotide, pentamidine, perphenazine, pimozide, probucol, procainamide, prochlorperazine, protriptyline, quetiapine, quinidine, risperidone, salmeterol, sotalol, sparfloxacin, sumatriptan, tamoxifen, terfenadine, thioridazine, thiothixene, tizanidine, tocainide, trifluoperazine, trimethoprim, sulfamethoxazole, venlafaxine and zolmitriptan (claimed).

☐ 3. Document ID: JP 2002528497 W WO 200025778 A1 AU 9959947 A US 6255334 B1 NO 200102013 A BR 9914901 A EP 1126840 A1 US 20010020036 A1 KR 2001089363 A CN 1325304 A CZ 200101468 A3 MX 2001004297 A1 SK 200100552 A3 HU 200104696 A2 ZA 200103322 A

L5: Entry 3 of 6 File: DWPI Sep 3, 2002

DERWENT-ACC-NO: 2000-365373
DERWENT-WEEK: 200273

TITLE: A composition for the treatment of migraine, comprising metoclopramide; a 5HT1 receptor agonist, excluding zolmitriptan; and a carrier

INVENTOR: SANDS, G H; SANDE, G H

PRIORITY-DATA: 1998US-106328P (October 30, 1998), 1999US-0387990 (September 1, 1999), 2001US-0838440 (April 19, 2001)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
JP 2002528497 W	September 3, 2002		025	A61K045/00
WO 200025778 A1	May 11, 2000	E	018	A61K031/4045
AU 9959947 A	May 22, 2000		000	A61K031/4045
US 6255334 B1	July 3, 2001		000	A61K031/40
NO 200102013 A	April 24, 2001		000	A61K000/00
BR 9914901 A	July 17, 2001		000	A61K031/4045
EP 1126840 A1	August 29, 2001	E	000	A61K031/4045
US 20010020036 A1	September 6, 2001		000	A61K031/4045
KR 2001089363 A	October 6, 2001		000	A61K031/404
CN 1325304 A	December 5, 2001		000	A61K031/4045
CZ 200101468 A3	April 17, 2002		000	A61K031/4045
MX 2001004297 A1	August 1, 2001		000	A61K031/166
SK 200100552 A3	May 9, 2002		000	A61K031/4045
HU 200104696 A2	May 28, 2002		000	A61K031/4045
ZA 200103322 A	August 28, 2002		031	A61K000/00

200103322 A INT-CL (IPC): A61 K 0/00; A61 K 31/16; A61 K 31/166; A61 K 31/40; A61 K 31/404; A61 K 31/4045; A61 K 31/4196; A61 K 31/445; A61 K 31/454; A61 K 45/00; A61 P 25/06; C07 D 209/14; C07 D 401/00; C07 D 403/06

ABSTRACTED-PUB-NO: US 6255334B
BASIC-ABSTRACT:

NOVELTY - A composition for the treatment of migraine, comprising metoclopramide; a 5HT1 receptor agonist, excluding zolmitriptan; and a carrier.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM exists for a method of treating migraine, comprising administering a composition comprising metoclopramide; a 5HT1 receptor agonist, excluding zolmitriptan; and a carrier.

USE - Compositions comprising metoclopramide and a 5HT1 receptor agonist are useful for treating migraine.

ADVANTAGE - The compositions have increased efficacy against migraine and less nausea than with currently used therapies.
ABSTRACTED-PUB-NO:

US20010020036A EQUIVALENT-ABSTRACTS:

NOVELTY - A composition for the treatment of migraine, comprising metoclopramide; a 5HT1 receptor agonist, excluding zolmitriptan; and a carrier.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM exists for a method of treating migraine, comprising administering a composition comprising metoclopramide; a 5HT1 receptor agonist, excluding zolmitriptan; and a carrier.

USE - Compositions comprising metoclopramide and a 5HT1 receptor agonist are useful for treating migraine.

ADVANTAGE - The compositions have increased efficacy against migraine and less nausea than with currently used therapies.

NOVELTY - A composition for the treatment of migraine, comprising metoclopramide; a 5HT1 receptor agonist, excluding zolmitriptan; and a carrier.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM exists for a method of treating migraine, comprising administering a composition comprising metoclopramide; a 5HT1 receptor agonist, excluding zolmitriptan; and a carrier.

USE - Compositions comprising metoclopramide and a 5HT1 receptor agonist are useful for treating migraine.

ADVANTAGE - The compositions have increased efficacy against migraine and less nausea

than with currently used therapies.

WO 200025778A

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Clip Img | Image

☐ 4. Document ID: GB 2324961 A

L5: Entry 4 of 6 File: DWPI Nov 11, 1998

DERWENT-ACC-NO: 1998-545220
DERWENT-WEEK: 199847

TITLE: Composition for the treatment of migraine and related conditions - comprises neuropeptide Y or an agonist of the NPY receptor in combination with a 5-HT receptor agonist

INVENTOR: HARGREAVES, R J; WILLIAMSON, D J

PRIORITY-DATA: 1997GB-0009815 (May 14, 1997)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
GB 2324961 A	November 11, 1998		011	A61K038/16

INT-CL (IPC): A61 K 38/16

ABSTRACTED-PUB-NO: GB 2324961A
BASIC-ABSTRACT:

Composition (I) comprises neuropeptide Y (NPY) or an agonist of the NPY receptor in combination with a 5-HT1b/1d receptor agonist.

The 5-HT1b/1d receptor agonist is preferably sumatriptan, naratriptan, zolmitriptan, rizatriptan, eletriptan, almotriptan, or one of their salts, especially rizatriptan benzoate.

USE - (I) is used in the treatment and prevention of migraine and related conditions (claimed). the related conditions include cluster headache, chronic paroxysmal haemicrania, headache associated with vascular disorders, tension headache and paediatric migraine.

ADVANTAGE - (I) reduces the diameter of painfully distended cranial blood vessels.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

☐ 5. Document ID: GB 2315673 A

L5: Entry 5 of 6 File: DWPI Feb 11, 1998

DERWENT-ACC-NO: 1998-089560
DERWENT-WEEK: 199809

TITLE: Treating migraine - by co-administration of local anaesthetic e.g. lidocaine and serotonin 1D agonist e.g. rizatriptan

(12) UK Patent Application (19) GB (11) 2 324 961 (13) A

(43) Date of A Publication 11.11.1998

(21) Application No 9809555.7

(22) Date of Filing 05.05.1998

(30) Priority Data
(31) 9709815 (32) 14.05.1997 (33) GB

(51) INT CL[6]
A61K 38/16

(52) UK CL (Edition P)
A5B BHA B31X B31Y
U1S S2415

(56) Documents Cited
Chemical Abstracts 127:108941 & WO 97/20823 A2
BIOSIS Accession No: 97143848 & Headache 34(1), pages 35-40 (1994)

(58) Field of Search
ONLINE: CAS-ONLINE, DIALINDEX(MEDICINE), WPI

(71) Applicant(s)
Merck Sharp & Dohme Limited
(Incorporated in the United Kingdom)
Hertford Road, HODDESDON, Hertfordshire, EN11 9BU, United Kingdom

(72) Inventor(s)
Richard John Hargreaves
David John Williamson

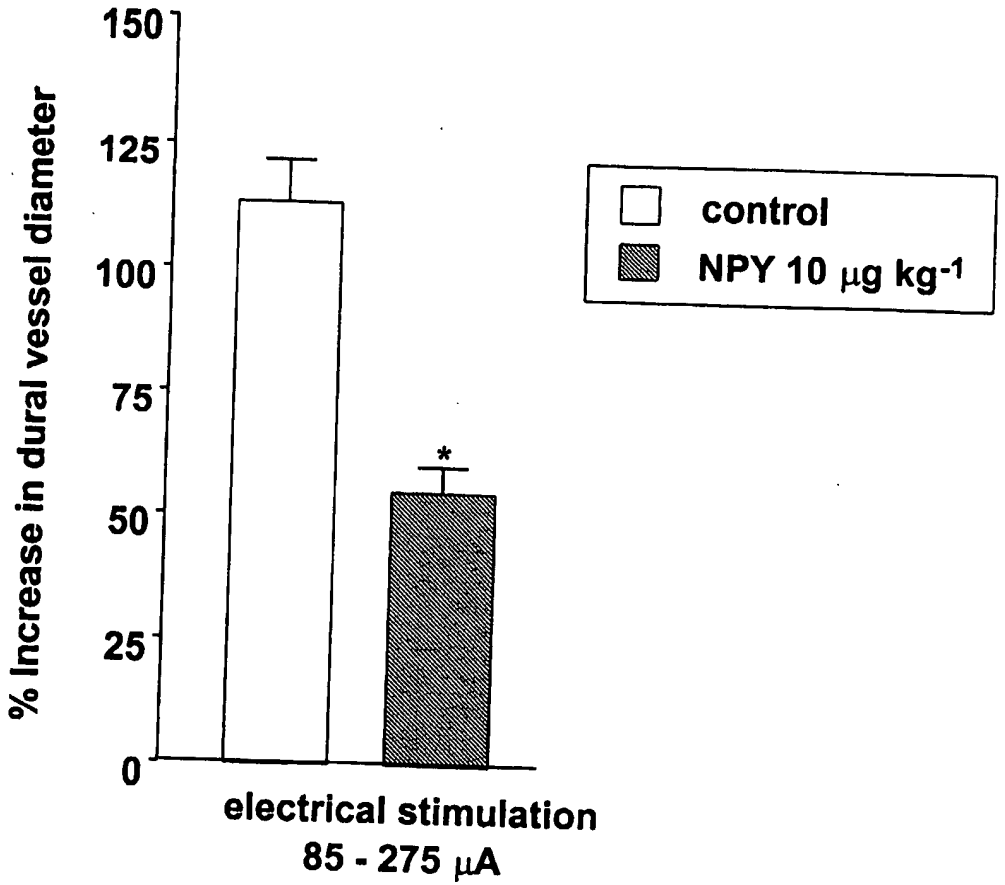
(74) Agent and/or Address for Service
J Thompson
Merck & Co Inc, European Patent Department, Terlings Park, Eastwick Road, HARLOW, Essex, CM20 2QR, United Kingdom

(54) Abstract Title
Use of neuropeptide Y receptor agonists for treating migraine

(57) Compounds which are agonists of the neuropeptide Y (NPY) receptor, including NPY itself, are effective agents in the treatment and/or prevention of migraine and associated conditions.

GB 2 324 961 A

Figure 1


150
125
100
75
50
25
0
% Increase in dural vessel diameter
*
control
NPY 10 μg kg-1
electrical stimulation
85 - 275 μA

2324961

USE OF NEUROPEPTIDE Y RECEPTOR AGONISTS FOR TREATING MIGRAINE

The present invention relates to a new use for neuropeptide Y (NPY) or an agonist of the NPY receptor. More particularly, the invention concerns the use of NPY or compounds which are agonists for the NPY receptor in the treatment and/or prevention of migraine and associated conditions.

Neuropeptide Y (NPY) is a 36-residue amidated peptide. It is anatomically co-distributed and co-released with noradrenaline in and from sympathetic postganglionic neurones. Stimulation of the sympathetic nervous system under physiological circumstances such as exercise or exposure to the cold promotes an elevation of both noradrenaline and NPY.

NPY is believed to act in the regulation of appetite control and vascular smooth muscle tone, as well as in the regulation of blood pressure. NPY also decreases cardiac contractility. Congestive heart failure and cardiogenic shock are believed to be associated with release of NPY into the bloodstream. Regulation of NPY levels may thus be beneficial in the management of these disease states.

At the cellular level, NPY binds to a G-protein coupled receptor. At least five subtypes of the NPY receptor family have been isolated and assigned on the basis of their pharmacological and physiological properties. The Y1 receptor subtype is stimulated by NPY or peptide YY (PYY) and appears to be the major vascular NPY receptor subtype. The DNA encoding the Y1 subtype has been cloned (WO 93/09227) and shown to encode a G-protein coupled receptor (Larhammar *et al.*, *J. Biol Chem.*, 1992, **267**, 10935; and Herzog *et al.*, *Proc. Natl. Acad. Sci. USA*, 1992, **89**, 5794). The Y2 receptor subtype is stimulated by C-terminal fragments of NPY or PYY and is abundantly expressed both centrally and peripherally. The DNA encoding the Y2 subtype has been isolated by expression cloning

(WO 95/21245). The Y3 receptor subtype is exclusively responsive to NPY and has been shown to occur in adrenal medulla, heart and brain stem. More recently, the Y4 (WO 95/17906) and Y5 (WO 96/16542) subtypes of the NPY receptor have been isolated by molecular cloning techniques. Further subtypes of the NPY receptor family are predicted to exist, based on pharmacological and physiological evidence.

NPY is involved in the regulation of eating behaviour, and is known to be an extremely potent orixigenic agent. When administered intracerebroventricularly or injected into the hypothalamic paraventricular nucleus (PVN) it elicits eating in satiated rats, and intraventricular injection of antisera to NPY decreases eating behaviour. NPY has been shown to stimulate appetite in a variety of species and at different stages of development. Other effects on energy metabolism include decreased thermogenesis and body temperature, and increased white fat storage and lipoprotein lipase activity. NPY levels in the PVN increase upon fasting, before scheduled meals, and in both streptozotocin-induced and spontaneous diabetes. In addition, NPY levels are elevated in genetically obese and hyperphagic Zucker rats. It has accordingly been suggested that agents which are ligands for the appropriate NPY receptor subtype might be effective in the treatment of obesity and diabetes, and eating disorders such as anorexia and bulimia.

Other disorders for which therapeutic treatment with a suitable NPY receptor ligand has been proposed include anxiety, hypertension, cocaine withdrawal, congestive heart failure, memory deficits, cardiac and cerebral vasospasm, pheochromocytoma and ganglioneuroblastoma, as well as Huntington's, Alzheimer's and Parkinson's diseases.

Nowhere in the prior art available to date, however, has there been any disclosure or suggestion that NPY or an agonist of NPY receptors might be beneficial in the treatment and/or prevention of migraine and associated conditions.

Although the precise mechanisms involved in the pathogenesis of

migraine are not fully understood, it is generally recognised that headache pain is vascular in origin, probably arising from blood vessels of the dura mater and large cerebral arteries. Cranial blood vessels are densely innervated by trigeminal sensory neurones that have been shown to contain the potent vasodilator and pro-inflammatory peptide, calcitonin gene-related peptide (CGRP), and the inflammatory neurokinins, substance P and neurokinin A. In animals, stimulation of trigeminal nerve fibres evokes vasodilation and plasma protein extravasation within the dura mater, presumably mediated via release of these pro-inflammatory neuropeptides. Clinically effective anti-migraine drugs, such as the ergot alkaloids and sumatriptan, have been found to inhibit neurogenic extravasation within the dura evoked by stimulation of the trigeminal ganglion but not extravasation evoked by substance P injection, suggesting that they block neurogenic extravasation by a presynaptic action to inhibit the release of neuropeptides (Saito *et al.*, *Ann. Neurol.*, 1988, **24**, 732; and Buzzi & Moskowitz, *Br. J. Pharmacol.*, 1990, **99**, 202). This effect, mediated via activation of 5-$HT_{1B/1D}$ receptors located on the trigeminal sensory nerve endings, has been suggested as a possible mechanism by which these compounds exert their anti-migraine action (Buzzi & Moskowitz, *Cephalalgia*, 1991, **11**, 165). It is believed that 5-$HT_{1B/1D}$ agonists such as sumatriptan confer their therapeutic action by reducing the diameter of painfully distended cranial blood vessels (Humphrey & Feniuk, *Trends Pharmacol. Sci.*, 1991, **12**, 444).

Using the recently-developed technique of direct measurement of dural vessel diameter in the rat using intravital microscopy (Williamson *et al.*, *Br. J. Pharmacol.*, 1996, **117**, 271P), it has now been found, surprisingly, that intravenous administration of NPY is capable of blocking neurogenic vasodilation in the dura mater. This finding demonstrates that NPY or an agonist of the NPY receptor can be of benefit in the treatment and/or prevention of migraine and associated conditions, including cluster headache, chronic paroxysmal hemicrania, headache

associated with vascular disorders, tension headache and paediatric migraine.

The present invention accordingly provides the use of NPY or an agonist of the NPY receptor for the manufacture of a medicament for the treatment and/or prevention of migraine and associated conditions.

The present invention also provides a method for the treatment and/or prevention of migraine and associated conditions, which method comprises administering to a patient in need of such treatment an effective amount of NPY or an agonist of the NPY receptor.

As discussed above, five discrete subtypes (Y1 to Y5) of the neuropeptide Y receptor have been isolated and characterized to date. The expression "agonist of the NPY receptor" as used herein will accordingly be understood to relate to compounds which are selective agonists of one or more of the NPY receptor subtypes relative to the other subtypes, or to compounds which are non-selective agonists of the NPY receptor. Indeed, as will be appreciated, NPY itself is an example of a compound which interacts non-selectively with the various subtypes of the NPY receptor.

Agonists of the NPY receptor of use in the present invention may be any NPY receptor agonists known from the art. Representative classes of specific compounds which are agonists of the NPY receptor are described, for example, in WO 96/40660; WO 96/14307; WO 95/00161; WO 94/00486; US-5,569,742; EP-A-0355793; JP-A-06116284; and CA-A-2134428.

For the effective treatment and/or prevention of migraine and associated conditions, a pharmaceutical composition may be provided which comprises NPY or an agonist of the NPY receptor in association with a pharmaceutically acceptable carrier. Suitable pharmaceutical compositions may conveniently be adapted for administration orally, rectally or parenterally, e.g. intravenously. For oral adminstration, the formulation may be presented in the form of tablets, pills, capsules, powders or granules; for parenteral administration, sterile parenteral solutions or suspensions may conveniently be utilised; and for rectal

administration, the formulation may conveniently be presented in the form of suppositories.

The compositions may be formulated by conventional methods well known in the pharmaceutical art, for example as described in *Remington: The Science and Practice of Pharmacy*, Mack Publishing Company, 19th Edition, 1995.

For use in the treatment and/or prevention of migraine and associated conditions, NPY or an agonist of the NPY receptor may suitably be administered at a daily dosage of about 0.001 to 100 mg/kg, typically about 0.002 to 10 mg/kg, more particularly about 0.005 to 1.0 mg/kg, and especially about 0.01 to 0.1 mg/kg. The active ingredient will typically be administered on a regimen of 1 to 4 times per day.

If desired, NPY or an agonist of the NPY receptor as defined herein may be co-administered with another medicament, in particular a known anti-migraine agent which elicits its effects by activating the 5-$HT_{1B/1D}$ receptor. In this context, examples of specific 5-$HT_{1B/1D}$ receptor agonists include sumatriptan (described in GB 2,162,522), naratriptan (GB 2,208,646), zolmitriptan (WO 91/18897), rizatriptan (EP 0,497,512), eletriptan (WO 92/06973) and almotriptan (WO 94/02460). When co-administered, the combination of a 5-$HT_{1B/1D}$ receptor agonist and of NPY or an agonist of the NPY receptor may be presented in a ratio which is consistent with the manifestation of the desired effect. In particular, the molar ratio of the 5-$HT_{1B/1D}$ receptor agonist to NPY or to the agonist of the NPY receptor will suitably be approximately 1 to 1. Preferably, this ratio will be between 0.001 to 1 and 1000 to 1, and especially from 0.01:1 to 100:1. The 5-$HT_{1B/1D}$ receptor agonist will suitably be administered in a standard dosage known from the art to elicit an acceptable anti-migraine effect.

Specific aspects of the invention will now be described with reference to the accompanying drawing, Figure 1, which shows the effect

of neuropeptide Y on neurogenic vasodilation of dural blood vessels in the anaesthetised rat.

Surgical preparation

Male Sprague-Dawley rats (300-400 g) were anaesthetised throughout terminal experiments with pentobarbitone sodium (initially 60 mg kg^{-1} i.p., then 18 mg kg^{-1} hr^{-1}, continuous i.v. infusion). A femoral artery and both femoral veins were cannulated to record blood pressure, for intravenous injection of drugs and for infusion of anaesthetic, respectively. Rats were placed in a stereotaxic frame, the skull exposed and the right parietal bone thinned by drilling with a saline-cooled drill, until the blood vessels of the dura were clearly visible through the intact skull. The cranial window was covered in mineral oil (37 °C) and a branch of the middle meningeal artery viewed using an intravital microscope (Microvision MV2100, UK) and the image displayed on a television monitor. Dural blood vessel diameter was continuously measured using a video dimension analyser (Living Systems Instrumentation, USA) and displayed with mean arterial blood pressure (MABP) on a chart recorder and a data analysis system (MI^2, Modular Instruments, UK). A bipolar stimulating electrode (NE 200X, Clark Electromedical) was placed on the surface of the cranial window approximately 200 μm from the vessel of interest.

Experimental protocol

Prior to the start of experiments the surface of the cranial window was stimulated at 5 Hz, 1 ms for 10 seconds (Grass S88 stimulator, Grass Instruments, USA) with increasing voltage until an intensity was reached at which a maximal dilation was observed. The stimulus current delivered was also measured by voltage drop across a resistance using an oscilloscope.

In neurogenic vasodilation studies an initial control dilation was performed followed by 2 further stimulations at 20 minute intervals. NPY

was injected intravenously at 1 μg kg^{-1} and 10 μg kg^{-1} (over 1 minute) 15 min prior to the second and third stimulations, respectively.

Data analysis

Dural vasodilation evoked by electrical stimulation of the cranial window was calculated as percentage increase in vessel diameter from baseline. Values presented are means ± sem. The effect of NPY on neurogenic vasodilation was assessed by comparing the control responses to those evoked after drug treatment using ANOVA and paired t-tests (BMDP statistical software). In addition, to investigate the effect of NPY on dural vessel diameter *per se* the actual diameter values (in arbitrary units) prior to control and subsequent dilations were compared using ANOVA and paired t-tests. The effects of NPY (10 μg kg^{-1}) on MABP were calculated as percentage changes from the pre-NPY baseline MABP. Values of less than 0.05 were considered to be statistically significant.

Effect of NPY on neurogenic vasodilation (Fig. 1)

Electrical stimulation (85-275 μA) of the cranial window elicited a 113 ± 9 % (n = 6) increase in dural blood vessel diameter. Pretreatment with NPY at a dose of 10 μg kg^{-1}, i.v. elicted a 55 ± 5 % increase in diameter, which represented a 51 % inhibition in neurogenic vasodilation as compared to control.

Conclusion

These studies demonstrate that NPY selectively inhibits neurogenic vasodilation of dural blood vessels in the anaesthetised rat.

CLAIMS:

1. The use of neuropeptide Y (NPY) or an agonist of the NPY receptor for the manufacture of a medicament for the treatment and/or prevention of migraine and associated conditions.

2. The use as claimed in claim 1 wherein the medicament is adapted for co-administration of a 5-$HT_{1B/1D}$ receptor agonist.

3. The use as claimed in claim 2 wherein the 5-$HT_{1B/1D}$ receptor agonist is sumatriptan, naratriptan, zolmitriptan, rizatriptan, eletriptan or almotriptan, or a pharmaceutically acceptable salt thereof.

4. The use as claimed in claim 3 wherein the 5-$HT_{1B/1D}$ receptor agonist is rizatriptan benzoate.

5. A pharmaceutical composition comprising neuropeptide Y (NPY) or an agonist of the NPY receptor in combination with a 5-$HT_{1B/1D}$ receptor agonist.

6. A composition as claimed in claim 5 wherein the 5-$HT_{1B/1D}$ receptor agonist is sumatriptan, naratriptan, zolmitriptan, rizatriptan, eletriptan or almotriptan, or a pharmaceutically acceptable salt thereof.

7. A composition as claimed in claim 6 wherein the 5-$HT_{1B/1D}$ receptor agonist is rizatriptan benzoate.

The Patent Office

1

Applicati n N : GB 9809555.7
Claims searched: 1-7

Examiner: John Jenkins
Date of search: 29 July 1998

Patents Act 1977
Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK Cl (Ed.P):

Int Cl (Ed.6):

Other: ONLINE: CAS-ONLINE, DIALINDEX(MEDICINE), WPI

Documents considered to be relevant:

Category	Identity of document and relevant passage	Relevant to claims
A	Chemical Abstracts 127:108941 & WO 97/20823 A2 (NOVARTIS AG)	
A	BIOSIS Accession No: 97143848 & Headache 34(1) pages 35-40 (1994) (V GALLAI et al)	

X Document indicating lack of novelty or inventive step
Y Document indicating lack of inventive step if combined with one or more other documents of same category.
& Member of the same patent family

A Document indicating technological background and/or state of the art.
P Document published on or after the declared priority date but before the filing date of this invention.
E Patent document published on or after, but with priority date earlier than, the filing date of this application.

INVENTOR: SANDQUIST, E; SIMITCHIEVA, K S

PRIORITY-DATA: 1996GB-0017896 (August 28, 1996), 1996US-022899P (August 1, 1996)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
GB 2315673 A	February 11, 1998		025	A61K031/41

INT-CL (IPC): A61 K 31/165; A61 K 31/41; A61 K 31:165; A61 K 31:40

ABSTRACTED-PUB-NO: GB 2315673A
BASIC-ABSTRACT:

A method of treating migraine comprises co-administration of a local anaesthetic and a serotonin 1D agonist (5-HT1D agonist).

The local anaesthetic is preferably selected from benzocaine, mepivacaine, bupivacaine, cocaine, lidocaine or prilidocaine and their salts, acids and bases and is especially lidocaine hydrochloride. The 5-HT1D agonist is selected from rizatriptan, sumitriptin, naratriptin or zolmitriptan and is especially rizatriptan. The formulation preferably contains 1-35 mg rizatriptan and 1-3 mg lidocaine in an intranasal carrier with a volume of 0.1-1.0 ml.

ADVANTAGE - The local anaesthetic has a vasodilative effect which enhances the absorption of the 5-HT1D agonist, leading to faster distribution and onset of action.

☐ 6. Document ID: WO 9802186 A1 KR 2000023708 A ZA 9706178 A AU 9734551 A CN 1225018 A BR 9710241 A CN 1230123 A AU 712546 B JP 2000505090 W KR 2000022239 A

L5: Entry 6 of 6 File: DWPI Jan 22, 1998

DERWENT-ACC-NO: 1998-145223
DERWENT-WEEK: 200107

TITLE: New inclusion complex used to treat migraine and cluster headaches - comprises indole selective serotonin agonist and cyclodextrin

INVENTOR: DE KOCK, L; WHITTAKER, D V ; PENKLER, L J

PRIORITY-DATA: 1996ZA-0005889 (July 11, 1996)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
WO 9802186 A1	January 22, 1998	E	029	A61K047/48
KR 2000023708 A	April 25, 2000		000	A61K047/48
ZA 9706178 A	April 29, 1998		026	C08B000/00
AU 9734551 A	February 9, 1998		000	A61K047/48
CN 1225018 A	August 4, 1999		000	A61K047/48
BR 9710241 A	August 10, 1999		000	A61K047/48
CN 1230123 A	September 29, 1999		000	A61K047/48
AU 712546 B	November 11, 1999		000	A61K047/48
JP 2000505090 W	April 25, 2000		026	A61K031/404
KR 2000022239 A	April 25, 2000		000	A61K047/48

INT-CL (IPC): A61 K 9/00; A61 K 9/70; A61 K 31/404; A61 K 47/40; A61 K 47/48; A61 P 25/06; C07 D 0/00; C08 B 0/00

ABSTRACTED-PUB-NO: WO 9802186A
BASIC-ABSTRACT:

A new inclusion complex comprises (a) an indole selective serotonin (5-HT-1D) agonist or a salt thereof and (b) an optionally substituted beta - or gamma -cyclodextrin.

(a) is sumatriptan, naratriptan, rizatriptan, zolmitriptan, eletriptan and almotriptan or their salts. (b) is 2-hydroxypropyl- beta -cyclodextrin, methylated - beta -cyclodextrin, sulphoalkylated beta -cyclodextrin, gamma -cyclodextrin, or 2-hydroxypropylated or methylated or sulphoalkylated derivatives of gamma -cyclodextrin.

USE - The new inclusion complex is used to treat migraine or cluster headaches. The complex is formulated for oral or nasal mucosal delivery.

ADVANTAGE - The complex allows for mucosal administration of the anti-migraine drug through the mucosal tissues of the mouth or nose and so avoids the problems associated with injection and oral administration i.e. slow onset of action, low bioavailability and poor compliance due to nausea and vomiting. The cyclodextrins help enhance penetration of the anti-migraine drug through the mucosal membranes.

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Term	Documents
(1 NOT 3).DWPI.	6
(L1 NOT L3).DWPI.	6

Display Format: rev Change Format

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U.S. APPLICATION NUMBER NO.	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
10/129,773	Alan Roy Dearn	ASZD-P01-617

INTERNATIONAL APPLICATION NO.	
PCT/GB00/04528	
I.A. FILING DATE	PRIORITY DATE
11/28/2000	12/03/1999

28120
ROPES & GRAY
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

CONFIRMATION NO. 7672

371 ACCEPTANCE LETTER

OC000000009543923

Date Mailed: 02/21/2003

NOTICE OF ACCEPTANCE OF APPLICATION UNDER 35 U.S.C 371 AND 37 CFR 1.494 OR 1.495

The applicant is hereby advised that the United States Patent and Trademark Office in its capacity as an Elected Office (37 CFR 1.495) , has determined that the above identified international application has met the requirements of 35 U.S.C. 371, and is ACCEPTED for national patentability examination in the United States Patent and Trademark Office.

The United States Application Number assigned to the application is shown above and the relevant dates are:

08/28/2002	08/28/2002
DATE OF RECEIPT OF 35 U.S.C. 371(c)(1), (c)(2) and (c)(4) REQUIREMENTS	DATE OF RECEIPT OF ALL 35 U.S.C. REQUIREMENTS

A Filing Receipt (PTO-103X) will be issued for the present application in due course. **THE DATE APPEARING ON THE FILING RECEIPT AS THE " FILING DATE" IS THE DATE ON WHICH THE LAST OF THE 35 U.S.C. 371 REQUIREMENTS HAS BEEN RECEIVED IN THE OFFICE. THIS DATE IS SHOWN ABOVE.** *The filing date of the above identified application is the international filing date of the international application (Article 11(3) and 35 U.S.C. 363).* Once the Filing Receipt has been received, send all correspondence to the Group Art Unit designated thereon.

The following items have been received:

- U.S. Basic National Fee
- Copy of IPE Report
- Copy of references cited in ISR
- Copy of the International Application
- Copy of the International Search Report
- Information Disclosure Statements
- Oath or Declaration
- Substitute Specification

Applicant is reminded that any communications to the United States Patent and Trademark Office must be mailed to the address given in the heading and include the U.S. application no. shown above (37 CFR 1.5)

PAULETTE R KIDWELL
Telephone: (703) 305-3656

PART 3 - OFFICE COPY

FORM PCT/DO/EO/903 (371 Acceptance Notice)

JC02 Rec'd PCT/PTO 09 MAY 2002

FORM PTO 1390 (REV 9-2001) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		ATTORNEY'S DOCKET NUMBER
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		ASZD-P01-617
		U.S. APPLICATION NO. (If known, see 37 CFR 1.5) 10/129773
INTERNATIONAL APPLICATION NO. PCT/GB00/04528	INTERNATIONAL FILING DATES 28/11/2000	PRIORITY DATE CLAIMED 3/12/1999
TITLE OF INVENTION PHARMACEUTICAL FORMULATIONS CONTAINING ZOLMITRIPTAN		
APPLICANT(S) FOR DO/EO/US Dearn et al.		

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [x] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing 35 U.S.C. 371
3. [ ] This is an express request to begin national examination procedures (35 U.S.C. 371 (f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. [x] The US has been elected by the expiration of 19 months from the priority date (PCT Article 31).
5. [x] A copy of the International Application as filed (35 U.S.C. 371 (c)(2))
   a. [ ] is attached hereto (required only if not communicated by the International Bureau).
   b. [x] has been communicated by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [ ] An English language translation of the International Application as filed (35 U.S.C. 371 (c)(2)).
   a. [ ] is attached hereto.
   b. [ ] has been previously submitted under 35 U.S.C. 154(d)(4).
7. [x] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. [ ] are attached hereto (required only if not communicated by the International Bureau).
   b. [ ] have been communicated by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [x] have not been made and will not be made.
8. [ ] An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. [ ] An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. [ ] An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. [x] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [ ] A FIRST preliminary amendment.
14. [ ] A SECOND or SUBSEQUENT preliminary amendment.
15. [x] A substitute specification.
16. [ ] A change of power of attorney and/or address letter.
17. [ ] A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
18. [x] A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. [ ] A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
20. [x] Other items or information: Marked-up Copy of Specification

JC13 Rec'd PCT/PTO 09 MAY 2002

U.S. APPLICATION NO. (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
10/129773	PCT/GB00/04528	ASZD-P01-617

21. [x] The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) – (5)):

		CALCULATIONS PTO USE ONLY
[ ]	Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO $1040.00	
[x]	International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO $890.00	
[ ]	International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO $740.00	
[ ]	International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) $710.00	
[ ]	International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) $100.00	

ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 890.00	
Surcharge of $____ for furnishing the oath or declaration later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).	$	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	57-20 =	37	x 18.00	$	666.00
Independent claims	5-3 =	2	x 84.00	$	168.00
MULTIPLE DEPENDENT CLAIM(s) (if applicable)			+ 280.00	$	280.00
TOTAL OF ABOVE CALCULATIONS =				$	2,004.00
[ ] Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by ½.				$	
SUBTOTAL =				$	2,004.00
Processing fee of $____ for furnishing the English translation later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492 (f)). +				$	
TOTAL NATIONAL FEE =				$	2,004.00
Fee for recording the enclosed assignment (37 CFR 1.21 (h)). Assignment must be accompanied by appropriate cover sheet (37 CFR 3.28, 3.31) + (per property).				$	
TOTAL FEES ENCLOSED =				$	2,004.00
				Amount to be Refunded:	$
				Charged:	$

a. [ ] A check in the amount of $ ____ to cover the above fees is enclosed.

b. [x] Please charge my Deposit Account No. 18-1945 in the amount of $ 2,004.00 to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [x] The Commissioner is hereby authorized to charge any additional fees which may be required or credit any overpayment to my Deposit Account No. 18-1945. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

David P. Halstead, Ph.D.
ROPES & GRAY
One International Place
Boston, Massachusetts 02110-2624
(617) 951-7615

SIGNATURE:

David P. Halstead, Ph.D.
NAME

44,735
REGISTRATION NUMBER

SUBSTITUTE SPECIFICATION

PHARMACEUTICAL FORMULATIONS CONTAINING ZOLMITRIPTAN

RELATED APPLICATIONS

This application is a national stage filing under 35 U.S.C. 371 of PCT application PCT/GB00/04528, filed November 28, 2000, which claims priority from Great Britain Application No. 9928578.5, filed December 3, 1999, the specifications of each of which are incorporated by reference herein.

The present invention relates to new pharmaceutical formulations, their preparation and their use in treatment of disease. In particular the present invention relates to pharmaceutical formulations of the anti-migraine drug zolmitriptan for nasal application.

Zolmitriptan has the chemical name (S)-4-{{3-[2-(dimethylaminoethyl]-1H-indol-5-yl]methyl]-2-oxazolidinone. Zolmitriptan is a selective 5HT1-receptor agonist. The 5HT1-receptor mediates vasoconstriction and thus modifies blood flow to the carotid vascular bed. 5HT1-receptor agonists are beneficial in the treatment (including prophylaxis) of disease conditions wherein vasoconstriction in the carotid vascular bed is indicated, for example migraine, cluster headache and headache associated with vascular disorders, hereinafter referred to collectively as 'migraine'. Zolmitriptan has been developed for the acute treatment of migraine in the form of a 2.5 mg and 5 mg tablet intended to be taken up to a maximum of 15 mg per day.

Although zolmitriptan is a successful drug of considerable benefit to migraine sufferers, there is a continuing need for alternative methods for the direct treatment of migraine and the prophylactic treatment of migraine. In particular, patients suffering from migraine or the onset of migraine need fast relief of their suffering.

Zolmitriptan is a member of a class of drugs known as triptans, for example sumatriptan, naratriptan and rizatriptan, which are prescribed for the treatment of migraine. The leader in terms of sales is sumitriptan which has been marketed as an oral formulation. A subcutaneous formulation was also developed; this was more efficacious (P Tfelt-Hansen, Cephalalgia 1998, Vol 18(8), page 532-8) and gave a faster onset of action but was not so acceptable to the patient. An intranasal spray was also developed. This was more user-friendly than the subcutaneous injection but was reported to be less effective in reducing the symptoms of migraine attacks (C Dahlof, Cephalalgia 1998; 18(5): 278-282). Also, many patients reported an unpleasant bitter taste after using the nasal spray.

The present inventors sought a formulation of zolmitriptan that achieved fast relief whilst maintaining high efficacy. They also sought a formulation that, for the wide variety of patients that suffer from migraines, had a more acceptable route of administration than a subcutaneous injection. Clearly, the thought of a subcutaneous injection may dissuade many patients from taking appropriate and necessary treatment. Furthermore, the inventors sought

a formulation that was convenient, effective and acceptable to the patient and did not cause any unnecessary irritancy or side-effects.

USP5466699 discloses a class of chemical compounds for the treatment and prophylaxis of migraine. USP5466699 discloses that this class of compounds may be formulated for oral, sublingual, buccal, parenteral (for example subcutaneous, intramuscular or intraveneous), rectal, topical and intranasal administration and examples of such possible formulations, including an example of an intranasal formulation, are disclosed. The intranasal formulation consists of an active ingredient, methyl hydroxybenzoate (0.2%), propyl hydroxybenzoate (0.02%), citrate buffer and sufficient hydrochloric acid to take the pH to 7.

The present inventors devised an intranasal formulation of zolmitriptan that provided effective and improved fast relief for migraine sufferers. Although, the inventors do not wish to be bound by theory, it is thought that this is at least partly due to the direct mucosal absorption of a significant proportion of zolmitriptan administered by the intranasal route.

Furthermore, studies with an intranasal formulation of zolmitriptan having a pH of above 7.0, at a pH of 7.4, showed the stability of that formulation would not be acceptable over extended periods of time.

The present inventors provided an improved rapid onset of action with a stable intranasal formulation of zolmitriptan having a pH of below 7.0. In addition, this formulation was acceptable to the general patient population and did not cause unnecessary irritancy or side effects.

Accordingly the present inventors provide a pharmaceutical formulation suitable for intranasal administration which comprises zolmitriptan and a pharmaceutically acceptable carrier wherein the pH of the formulation is less than 7.0.

The zolmitriptan formulation for intranasal administration is generally prepared as an aqueous formulation and typically is buffered. Suitable buffering agents include citric acid, phosphates such as disodium phosphate (for example the dodecahydrate, heptahydrate, dihydrate and anhydrous forms) or sodium phosphate and mixtures thereof (for example McIlvaine's buffer which is a mixture of citric acid and disodium phosphate).

In a particular aspect the pH of the pharmaceutical formulation of zolmitriptan is below 6.0, for example in the range 3.5 to 5.5, and in particular in the range 4.5 to 5.5. In a particular aspect the pH of the formulation is about 5.0.

In addition to the buffer, the zolmitriptan formulation may contain other ingredients typically found in intranasal formulations, such as antioxidants for example sodium metabisulphite, taste-masking agents such as menthol and sweetening agents for example dextrose, glycerol, saccharin and sorbitol.

In another aspect the present invention provides an aqueous solution of zolmitriptan in a buffer at a pH of less than 7.0 in particular at a pH below 6.0, for example in the range 3.5 to 5.5 and in particular in the range 4.5 to 5.5, for example at about 5.0. In particular the present invention provides an aqueous solution of zolmitriptan in a buffer of citric acid and phosphate at a pH of less than 7.0, in particular at a pH below 6.0, for example in the range 3.5 to 5.5 and in particular in the range 4.5 to 5.5, for example at about 5.0.

The pharmaceutical formulation of the present invention may be co-administered (simultaneously or sequentially) with one or more pharmaceutical agents of value in treating migraine or related disease conditions.

The pharmaceutical formulations of the invention will normally be administered to humans so that, for example a unit dose of about 0.5 mg to 15 mg (for example 0.5 mg, 1.0 mg, 2.5 mg, 5.0 mg and 10mg) of zolmitriptan is delivered to the patient in need thereof. The concentration and volume of the formulation may vary as known in the intranasal art, typically a volume of 50 to 250µl is administered, for example 50µl or 100µl (in one spray or in two 50µl sprays - one for each nostril), The precise dose delivered depends on various factors known in the art including the weight, age and sex of the patient being treated and on the particular migraine disease condition being treated. Such a unit dose may be taken at any stage in the onset of, or during the course of, a migraine attack. Such a unit dose may be taken as needed, typically from 1 to 3 times a day.

The pharmaceutical formulations of this invention may be prepared by dissolving zolmitriptan in an acidic medium, for example aqueous citric acid, thereby forming the citrate salt of zolmitriptan, and taking the pH to the desired value by adding a suitable agent for example a phosphate. The resultant buffered solution is typically manufactured to ensure that it contains a low bioburden or to ensure that it is sterile. Typically the solution is sterilised for example by passing through a sterile filter (for example 0.2 µm) or by autoclaving. Preferably, the solution is purged with nitrogen, and overlaid with nitrogen in the primary pack, to minimise the possibility of degradation. Alternatively, another inert gas, such as argon, could be used. Therefore in another aspect the present invention provides a sterile

pharmaceutical formulation suitable for intranasal administration which comprises zolmitriptan and a pharmaceutically acceptable carrier wherein the pH of the formulation is less than 7.0.

The pharmaceutical formulations of the invention are typically filled into a suitable administration device capable of delivering a unit dose amount of zolmitriptan to the patient in need thereof. Such administration devices include those available commercially and the device disclosed in UK Registered Design 2071555. Therefore in a another aspect, the present invention provides an intranasal administration device containing zolmitriptan and a pharmaceutically acceptable carrier wherein the pH of the formulation is less than 7.0.

The filled intranasal administration device may be packaged to provide protection from light. Accordingly in yet a further aspect, the present invention provides an intranasal administration device containing zolmitriptan and a pharmaceutically acceptable carrier in light-protecting packaging, for example in foil pouches. In an alternative aspect, the device itself is a dark colour to provide protection from light, for example, a dark blue colour.

Therefore in a further aspect the present invention provides a pharmaceutical formulation suitable for intranasal administration which comprises zolmitriptan and a pharmaceutically acceptable carrier wherein the pH of the formulation is less than 7.0 for use in a method of therapeutic treatment of the human or animal body.

In yet a further aspect the present invention provides a method of treating a disease condition wherein agonism of 5HT1-receptors is beneficial which comprises administering an effective amount of a pharmaceutical formulation suitable for intranasal administration which comprises zolmitriptan and a pharmaceutically acceptable carrier wherein the pH of the formulation is less than 7.0. The present invention also provides the use of zolmitriptan and a pharmaceutically acceptable carrier in the manufacture of a pharmaceutical formulation suitable for intranasal administration wherein the pH of the formulation is less than 7.0.

Zolmitriptan used in the formulations of the present invention may be prepared according to the disclosures of WO 91/18897 and WO 97/06162.

Examples 1-4

Zolmitriptan is dissolved in an aqueous solution of citric acid, 0.4M disodium phosphate dodecahydrate is added to pH 5.0 and water of injection is added to the desired volume. In this manner solutions with concentrations of zolmitriptan of 5 mg/mL, 10

mg/mL, 25 mg/mL and 50 mg/mL are prepared. The solution is filtered through a sterilizing grade filter (0.2 μm), and filled into USP/Ph Eur Type 1 glass vials (nominal spray volume 100μL) which are closed with chlorobutyl stoppers.

Table 1

Nasal Spray Nominal Strength	0.5 mg	1 mg	2.5 mg	5 mg
Solution Concentration	5 mg/ml	10 mg/ml	25 mg/ml	50 mg/ml
Zolmitriptan	0.5	1.0	2.5	5.0
Citric acid, anhydrous USP/Ph Eur	1.11	1.29	1.79	2.60
Disodium phosphate dodecahydrate USP/Ph Eur*	qs to pH 5.0	qs to pH 5.0	qs to pH 5.0	qs to pH 5.0
Water for Injections USP/Ph Eur	to 0.1 ml	to 0.1 ml	to 0.1 ml	to 0.1 ml

* Added as a 0.4 M solution of Disodium Phosphate Dodecahydrate Ph Eur/USP diluted with purified water USP/Ph Eur.

The vials are assembled into the unit dose nasal spray device disclosed in UK Registered Design 2071555. This device comprises a vial holder, an actuation device and a protection cap. The assembled device may be used to deliver unit doses of zolmitriptan of 0.5 mg, 1.0 mg, 2.5 mg or 5.0 mg in a single administration. The filled nasal spray device is packaged into a plastic tray and placed inside a carton to provide protection from the light.

Examples 5-8

Zolmitriptan is dissolved in an aqueous solution of citric acid, 0.4M disodium phosphate is added to pH 5.0 and water of injection is added to the desired volume. In this manner solutions with concentrations of zolmitriptan of 5 mg/mL, 10 mg/mL, 25 mg/mL and 50 mg/mL are prepared. The solution is filtered and filled into USP/Ph Eur Type 1 glass vials (nominal spray volume 100μL) which are closed with chlorobutyl stoppers.

Table 1

Nasal Spray Nominal Strength	0.5 mg	1 mg	2.5 mg	5 mg
Solution Concentration	5 mg/ml	10 mg/ml	25 mg/ml	50 mg/ml
Zolmitriptan	0.5	1.0	2.5	5.0
Citric acid, anhydrous USP/Ph Eur	1.11	1.29	1.79	2.60
Disodium phosphate USP/Ph Eur*	qs to pH 5.0	qs to pH 5.0	qs to pH 5.0	qs to pH 5.0
Purified Water USP/Ph Eur	to 0.1 ml	to 0.1 ml	to 0.1 ml	to 0.1 ml

* Added as a 0.4 M solution of Disodium Phosphate Ph Eur/USP diluted with purified water for injection.

The vials are autoclaved at 121°C for 15 minutes. They are then assembled into the unit dose nasal spray device disclosed in UK Registered Design 2071555. This device comprises a vial holder, an actuation device and a protection cap. The assembled device may be used to deliver unit doses of zolmitriptan of 0.5 mg, 1.0 mg, 2.5 mg or 5.0 mg in a single administration. The filled nasal spray device is packaged into a plastic tray and placed inside a carton to provide protection from the light.

Example 9

The patient removes the packaging from the nasal spray device, and then removes the protection cap. The patient then inserts the nozzle of the device into a nostril and actuates it to administer a single dose.

CLAIMS

1. A pharmaceutical formulation suitable for intranasal administration which comprises zolmitriptan and a pharmaceutically acceptable carrier wherein the pH of the formulation is less than 7.0.

2. A pharmaceutical formulation according to claim 1 wherein the pH of the formulation is in the range 4.5 to 5.5.

3. A pharmaceutical formulation according to claim 1 wherein the formulation is buffered.

4. A pharmaceutical formulation according to claim 2 wherein the formulation is buffered.

5. A pharmaceutical formulation according to claim 3 wherein the buffer is a mixture of citric acid and disodium phosphate.

6. A pharmaceutical formulation according to claim 4 wherein the buffer is a mixture of citric acid and disodium phosphate.

7. A pharmaceutical formulation according to claim 1 which is sterile.

8. A pharmaceutical formulation according to claim 2 which is sterile.

9. A pharmaceutical formulation according to claim 3 which is sterile.

10. A pharmaceutical formulation according to claim 4 which is sterile.

11. A pharmaceutical formulation according to claim 5 which is sterile.

12. A pharmaceutical formulation according to claim 6 which is sterile.

13. A process for preparing a sterile pharmaceutical formulation as defined in any one of claims 7-12 which comprises autoclaving.

14. A method of treating a disease condition wherein agonism of 5HT1-receptors is beneficial which comprises administering an effective amount of a pharmaceutical formulation as defined in any one of claims 1 to 12.

15. An intranasal administration device containing a pharmaceutical formulation as defined in any one of claims 1 to 12.

16. An intranasal administration device containing a pharmaceutical formulation as defined in any one of claims 1 to 12 when packaged to provide protection from light.

17. An aqueous solution of zolmitriptan in a buffer at a pH less than 7.0.

18. An aqueous solution of zolmitriptan in a buffer at a pH in the range 4.5 to 5.5.

19. A citrate salt of zolmitriptan.

20. A citrate salt of zolmitriptan in aqueous solution.

ABSTRACT

A pharmaceutical formulation of the 5HT1-agonist, zolmitriptan, for use in intranasal administration. The formulation is useful in treating migraine and related disorders.

MARKED-UP SPECIFICATION

PHARMACEUTICAL FORMULATIONS CONTAINING ZOLMITRIPTAN

RELATED APPLICATIONS

This application is a national stage filing under 35 U.S.C. 371 of PCT application PCT/GB00/04528, filed November 28, 2000, which claims priority from Great Britain Application No. 9928578.5, filed December 3, 1999, the specifications of each of which are incorporated by reference herein.

The present invention relates to new pharmaceutical formulations, their preparation and their use in treatment of disease. In particular the present invention relates to pharmaceutical formulations of the anti-migraine drug zolmitriptan for nasal application.

Zolmitriptan has the chemical name (S)-4-{{3-[2-(dimethylaminoethyl]-1H-indol-5-yl]methyl]-2-oxazolidinone. Zolmitriptan is a selective 5HT1-receptor agonist. The 5HT1-receptor mediates vasoconstriction and thus modifies blood flow to the carotid vascular bed. 5HT1-receptor agonists are beneficial in the treatment (including prophylaxis) of disease conditions wherein vasoconstriction in the carotid vascular bed is indicated, for example migraine, cluster headache and headache associated with vascular disorders, hereinafter referred to collectively as 'migraine'. Zolmitriptan has been developed for the acute treatment of migraine in the form of a 2.5 mg and 5 mg tablet intended to be taken up to a maximum of 15 mg per day.

Although zolmitriptan is a successful drug of considerable benefit to migraine sufferers, there is a continuing need for alternative methods for the direct treatment of migraine and the prophylactic treatment of migraine. In particular, patients suffering from migraine or the onset of migraine need fast relief of their suffering.

Zolmitriptan is a member of a class of drugs known as triptans, for example sumatriptan, naratriptan and rizatriptan, which are prescribed for the treatment of migraine. The leader in terms of sales is sumitriptan which has been marketed as an oral formulation. A subcutaneous formulation was also developed; this was more efficacious (P Tfelt-Hansen, Cephalalgia 1998, Vol 18(8), page 532-8) and gave a faster onset of action but was not so acceptable to the patient. An intranasal spray was also developed. This was more user-friendly than the subcutaneous injection but was reported to be less effective in reducing the symptoms of migraine attacks (C Dahlof, Cephalalgia 1998; 18(5): 278-282). Also, many patients reported an unpleasant bitter taste after using the nasal spray.

The present inventors sought a formulation of zolmitriptan that achieved fast relief whilst maintaining high efficacy. They also sought a formulation that, for the wide variety of patients that suffer from migraines, had a more acceptable route of administration than a subcutaneous injection. Clearly, the thought of a subcutaneous injection may dissuade many patients from taking appropriate and necessary treatment. Furthermore, the inventors sought

a formulation that was convenient, effective and acceptable to the patient and did not cause any unnecessary irritancy or side-effects.

USP5466699 discloses a class of chemical compounds for the treatment and prophylaxis of migraine. USP5466699 discloses that this class of compounds may be formulated for oral, sublingual, buccal, parenteral (for example subcutaneous, intramuscular or intraveneous), rectal, topical and intranasal administration and examples of such possible formulations, including an example of an intranasal formulation, are disclosed. The intranasal formulation consists of an active ingredient, methyl hydroxybenzoate (0.2%), propyl hydroxybenzoate (0.02%), citrate buffer and sufficient hydrochloric acid to take the pH to 7.

The present inventors devised an intranasal formulation of zolmitriptan that provided effective and improved fast relief for migraine sufferers. Although, the inventors do not wish to be bound by theory, it is thought that this is at least partly due to the direct mucosal absorption of a significant proportion of zolmitriptan administered by the intranasal route.

Furthermore, studies with an intranasal formulation of zolmitriptan having a pH of above 7.0, at a pH of 7.4, showed the stability of that formulation would not be acceptable over extended periods of time.

The present inventors provided an improved rapid onset of action with a stable intranasal formulation of zolmitriptan having a pH of below 7.0. In addition, this formulation was acceptable to the general patient population and did not cause unnecessary irritancy or side effects.

Accordingly the present inventors provide a pharmaceutical formulation suitable for intranasal administration which comprises zolmitriptan and a pharmaceutically acceptable carrier wherein the pH of the formulation is less than 7.0.

The zolmitriptan formulation for intranasal administration is generally prepared as an aqueous formulation and typically is buffered. Suitable buffering agents include citric acid, phosphates such as disodium phosphate (for example the dodecahydrate, heptahydrate, dihydrate and anhydrous forms) or sodium phosphate and mixtures thereof (for example McIlvaine's buffer which is a mixture of citric acid and disodium phosphate).

In a particular aspect the pH of the pharmaceutical formulation of zolmitriptan is below 6.0, for example in the range 3.5 to 5.5, and in particular in the range 4.5 to 5.5. In a particular aspect the pH of the formulation is about 5.0.

In addition to the buffer, the zolmitriptan formulation may contain other ingredients typically found in intranasal formulations, such as antioxidants for example sodium metabisulphite, taste-masking agents such as menthol and sweetening agents for example dextrose, glycerol, saccharin and sorbitol.

In another aspect the present invention provides an aqueous solution of zolmitriptan in a buffer at a pH of less than 7.0 in particular at a pH below 6.0, for example in the range 3.5 to 5.5 and in particular in the range 4.5 to 5.5, for example at about 5.0. In particular the present invention provides an aqueous solution of zolmitriptan in a buffer of citric acid and phosphate at a pH of less than 7.0, in particular at a pH below 6.0, for example in the range 3.5 to 5.5 and in particular in the range 4.5 to 5.5, for example at about 5.0.

The pharmaceutical formulation of the present invention may be co-administered (simultaneously or sequentially) with one or more pharmaceutical agents of value in treating migraine or related disease conditions.

The pharmaceutical formulations of the invention will normally be administered to humans so that, for example a unit dose of about 0.5 mg to 15 mg (for example 0.5 mg, 1.0 mg, 2.5 mg, 5.0 mg and 10mg) of zolmitriptan is delivered to the patient in need thereof. The concentration and volume of the formulation may vary as known in the intranasal art, typically a volume of 50 to 250µl is administered, for example 50µl or 100µl (in one spray or in two 50µl sprays - one for each nostril), The precise dose delivered depends on various factors known in the art including the weight, age and sex of the patient being treated and on the particular migraine disease condition being treated. Such a unit dose may be taken at any stage in the onset of, or during the course of, a migraine attack. Such a unit dose may be taken as needed, typically from 1 to 3 times a day.

The pharmaceutical formulations of this invention may be prepared by dissolving zolmitriptan in an acidic medium, for example aqueous citric acid, thereby forming the citrate salt of zolmitriptan, and taking the pH to the desired value by adding a suitable agent for example a phosphate. The resultant buffered solution is typically manufactured to ensure that it contains a low bioburden or to ensure that it is sterile. Typically the solution is sterilised for example by passing through a sterile filter (for example 0.2 µm) or by autoclaving. Preferably, the solution is purged with nitrogen, and overlaid with nitrogen in the primary pack, to minimise the possibility of degradation. Alternatively, another inert gas, such as argon, could be used. Therefore in another aspect the present invention provides a sterile

pharmaceutical formulation suitable for intranasal administration which comprises zolmitriptan and a pharmaceutically acceptable carrier wherein the pH of the formulation is less than 7.0.

The pharmaceutical formulations of the invention are typically filled into a suitable administration device capable of delivering a unit dose amount of zolmitriptan to the patient in need thereof. Such administration devices include those available commercially and the device disclosed in UK Registered Design 2071555. Therefore in a another aspect, the present invention provides an intranasal administration device containing zolmitriptan and a pharmaceutically acceptable carrier wherein the pH of the formulation is less than 7.0.

The filled intranasal administration device may be packaged to provide protection from light. Accordingly in yet a further aspect, the present invention provides an intranasal administration device containing zolmitriptan and a pharmaceutically acceptable carrier in light-protecting packaging, for example in foil pouches. In an alternative aspect, the device itself is a dark colour to provide protection from light, for example, a dark blue colour.

Therefore in a further aspect the present invention provides a pharmaceutical formulation suitable for intranasal administration which comprises zolmitriptan and a pharmaceutically acceptable carrier wherein the pH of the formulation is less than 7.0 for use in a method of therapeutic treatment of the human or animal body.

In yet a further aspect the present invention provides a method of treating a disease condition wherein agonism of 5HT1-receptors is beneficial which comprises administering an effective amount of a pharmaceutical formulation suitable for intranasal administration which comprises zolmitriptan and a pharmaceutically acceptable carrier wherein the pH of the formulation is less than 7.0. The present invention also provides the use of zolmitriptan and a pharmaceutically acceptable carrier in the manufacture of a pharmaceutical formulation suitable for intranasal administration wherein the pH of the formulation is less than 7.0.

Zolmitriptan used in the formulations of the present invention may be prepared according to the disclosures of WO 91/18897 and WO 97/06162.

Examples 1-4

Zolmitriptan is dissolved in an aqueous solution of citric acid, 0.4M disodium phosphate dodecahydrate is added to pH 5.0 and water of injection is added to the desired volume. In this manner solutions with concentrations of zolmitriptan of 5 mg/mL, 10

mg/mL, 25 mg/mL and 50 mg/mL are prepared. The solution is filtered through a sterilizing grade filter (0.2 μm), and filled into USP/Ph Eur Type 1 glass vials (nominal spray volume 100μL) which are closed with chlorobutyl stoppers.

Table 1

Nasal Spray Nominal Strength	0.5 mg	1 mg	2.5 mg	5 mg
Solution Concentration	5 mg/ml	10 mg/ml	25 mg/ml	50 mg/ml
Zolmitriptan	0.5	1.0	2.5	5.0
Citric acid, anhydrous USP/Ph Eur	1.11	1.29	1.79	2.60
Disodium phosphate dodecahydrate USP/Ph Eur*	qs to pH 5.0	qs to pH 5.0	qs to pH 5.0	qs to pH 5.0
Water for Injections USP/Ph Eur	to 0.1 ml	to 0.1 ml	to 0.1 ml	to 0.1 ml

* Added as a 0.4 M solution of Disodium Phosphate Dodecahydrate Ph Eur/USP diluted with purified water USP/Ph Eur.

The vials are assembled into the unit dose nasal spray device disclosed in UK Registered Design 2071555. This device comprises a vial holder, an actuation device and a protection cap. The assembled device may be used to deliver unit doses of zolmitriptan of 0.5 mg, 1.0 mg, 2.5 mg or 5.0 mg in a single administration. The filled nasal spray device is packaged into a plastic tray and placed inside a carton to provide protection from the light.

Examples 5-8

Zolmitriptan is dissolved in an aqueous solution of citric acid, 0.4M disodium phosphate is added to pH 5.0 and water of injection is added to the desired volume. In this manner solutions with concentrations of zolmitriptan of 5 mg/mL, 10 mg/mL, 25 mg/mL and 50 mg/mL are prepared. The solution is filtered and filled into USP/Ph Eur Type 1 glass vials (nominal spray volume 100µL) which are closed with chlorobutyl stoppers.

Table 1

Nasal Spray Nominal Strength	0.5 mg	1 mg	2.5 mg	5 mg
Solution Concentration	5 mg/ml	10 mg/ml	25 mg/ml	50 mg/ml
Zolmitriptan	0.5	1.0	2.5	5.0
Citric acid, anhydrous USP/Ph Eur	1.11	1.29	1.79	2.60
Disodium phosphate USP/Ph Eur*	qs to pH 5.0	qs to pH 5.0	qs to pH 5.0	qs to pH 5.0
Purified Water USP/Ph Eur	to 0.1 ml	to 0.1 ml	to 0.1 ml	to 0.1 ml

* Added as a 0.4 M solution of Disodium Phosphate Ph Eur/USP diluted with purified water for injection.

The vials are autoclaved at 121°C for 15 minutes. They are then assembled into the unit dose nasal spray device disclosed in UK Registered Design 2071555. This device comprises a vial holder, an actuation device and a protection cap. The assembled device may be used to deliver unit doses of zolmitriptan of 0.5 mg, 1.0 mg, 2.5 mg or 5.0 mg in a single administration. The filled nasal spray device is packaged into a plastic tray and placed inside a carton to provide protection from the light.

Example 9

The patient removes the packaging from the nasal spray device, and then removes the protection cap. The patient then inserts the nozzle of the device into a nostril and actuates it to administer a single dose.

CLAIMS

1. A pharmaceutical formulation suitable for intranasal administration which comprises zolmitriptan and a pharmaceutically acceptable carrier wherein the pH of the formulation is less than 7.0.

2. A pharmaceutical formulation according to claim 1 wherein the pH of the formulation is in the range 4.5 to 5.5.

3. A pharmaceutical formulation according to ~~either~~ claim 1 ~~or claim 2~~ wherein the formulation is buffered.

4. A pharmaceutical formulation according to claim 2 wherein the formulation is buffered.

~~4~~5. A pharmaceutical formulation according to claim 3 wherein the buffer is a mixture of citric acid and disodium phosphate.

6. A pharmaceutical formulation according to claim 4 wherein the buffer is a mixture of citric acid and disodium phosphate.

~~5~~7. A pharmaceutical formulation according to ~~any one of~~ claims 1 ~~to 4~~ which is sterile.

8. A pharmaceutical formulation according to claim 2 which is sterile.

9. A pharmaceutical formulation according to claim 3 which is sterile.

10. A pharmaceutical formulation according to claim 4 which is sterile.

11. A pharmaceutical formulation according to claim 5 which is sterile.

12. A pharmaceutical formulation according to claim 6 which is sterile.

~~6~~13. A process for preparing a sterile pharmaceutical formulation as defined in any one of claims ~~5~~7-12 which comprises autoclaving.

~~7~~14. A method of treating a disease condition wherein agonism of 5HT1-receptors is beneficial which comprises administering an effective amount of a pharmaceutical formulation as defined in any one of claims 1 to ~~5~~12.

~~8. The use of zolmitriptan in the manufacture of a pharmaceutical formulation as defined in any one of claims 1 to 5.~~

~~9~~15. An intranasal administration device containing a pharmaceutical formulation as defined in any one of claims 1 to ~~5~~12.

~~10~~16. An intranasal administration device containing a pharmaceutical formulation as defined in any one of claims 1 to ~~5~~12 when packaged to provide protection from light.

~~11~~17. An aqueous solution of zolmitriptan in a buffer at a pH less than 7.0.

~~12~~18. An aqueous solution of zolmitriptan in a buffer at a pH in the range 4.5 to 5.5.

~~13~~19. A citrate salt of zolmitriptan.

~~14~~20. A citrate salt of zolmitriptan in aqueous solution.

ABSTRACT

A pharmaceutical formulation of the 5HT1-agonist, zolmitriptan, for use in intranasal administration. The formulation is useful in treating migraine and related disorders.

ORIGINAL SPECIFICATION

PHARMACEUTICAL FORMULATIONS CONTAINING ZOLMITRIPTAN

The present invention relates to new pharmaceutical formulations, their preparation and their use in treatment of disease. In particular the present invention relates to pharmaceutical formulations of the anti-migraine drug zolmitriptan for nasal application.

Zolmitriptan has the chemical name (S)-4-{{3-[2-(dimethylaminoethyl]-1H-indol-5-yl]methyl]-2-oxazolidinone. Zolmitriptan is a selective 5HT1-receptor agonist. The 5HT1-receptor mediates vasoconstriction and thus modifies blood flow to the carotid vascular bed. 5HT1-receptor agonists are beneficial in the treatment (including prophylaxis) of disease conditions wherein vasoconstriction in the carotid vascular bed is indicated, for example migraine, cluster headache and headache associated with vascular disorders, hereinafter referred to collectively as 'migraine'. Zolmitriptan has been developed for the acute treatment of migraine in the form of a 2.5 mg and 5 mg tablet intended to be taken up to a maximum of 15 mg per day.

Although zolmitriptan is a successful drug of considerable benefit to migraine sufferers, there is a continuing need for alternative methods for the direct treatment of migraine and the prophylactic treatment of migraine. In particular, patients suffering from migraine or the onset of migraine need fast relief of their suffering.

Zolmitriptan is a member of a class of drugs known as triptans, for example sumatriptan, naratriptan and rizatriptan, which are prescribed for the treatment of migraine. The leader in terms of sales is sumitriptan which has been marketed as an oral formulation. A subcutaneous formulation was also developed; this was more efficacious (P Tfelt-Hansen, Cephalalgia 1998, Vol 18(8), page 532-8) and gave a faster onset of action but was not so acceptable to the patient. An intranasal spray was also developed. This was more user-friendly than the subcutaneous injection but was reported to be less effective in reducing the symptoms of migraine attacks (C Dahlof, Cephalalgia 1998; 18(5): 278-282). Also, many patients reported an unpleasant bitter taste after using the nasal spray.

The present inventors sought a formulation of zolmitriptan that achieved fast relief whilst maintaining high efficacy. They also sought a formulation that, for the wide variety of patients that suffer from migraines, had a more acceptable route of administration than a subcutaneous injection. Clearly, the thought of a subcutaneous injection may dissuade many patients from taking appropriate and necessary treatment. Furthermore, the inventors sought

a formulation that was convenient, effective and acceptable to the patient and did not cause any unnecessary irritancy or side-effects.

USP5466699 discloses a class of chemical compounds for the treatment and prophylaxis of migraine. USP5466699 discloses that this class of compounds may be formulated for oral, sublingual, buccal, parenteral (for example subcutaneous, intramuscular or intraveneous), rectal, topical and intranasal administration and examples of such possible formulations, including an example of an intranasal formulation, are disclosed. The intranasal formulation consists of an active ingredient, methyl hydroxybenzoate (0.2%), propyl hydroxybenzoate (0.02%), citrate buffer and sufficient hydrochloric acid to take the pH to 7.

The present inventors devised an intranasal formulation of zolmitriptan that provided effective and improved fast relief for migraine sufferers. Although, the inventors do not wish to be bound by theory, it is thought that this is at least partly due to the direct mucosal absorption of a significant proportion of zolmitriptan administered by the intranasal route.

Furthermore, studies with an intranasal formulation of zolmitriptan having a pH of above 7.0, at a pH of 7.4, showed the stability of that formulation would not be acceptable over extended periods of time.

The present inventors provided an improved rapid onset of action with a stable intranasal formulation of zolmitriptan having a pH of below 7.0. In addition, this formulation was acceptable to the general patient population and did not cause unnecessary irritancy or side effects.

Accordingly the present inventors provide a pharmaceutical formulation suitable for intranasal administration which comprises zolmitriptan and a pharmaceutically acceptable carrier wherein the pH of the formulation is less than 7.0.

The zolmitriptan formulation for intranasal administration is generally prepared as an aqueous formulation and typically is buffered. Suitable buffering agents include citric acid, phosphates such as disodium phosphate (for example the dodecahydrate, heptahydrate, dihydrate and anhydrous forms) or sodium phosphate and mixtures thereof (for example McIlvaine's buffer which is a mixture of citric acid and disodium phosphate).

In a particular aspect the pH of the pharmaceutical formulation of zolmitriptan is below 6.0, for example in the range 3.5 to 5.5, and in particular in the range 4.5 to 5.5. In a particular aspect the pH of the formulation is about 5.0.

In addition to the buffer, the zolmitriptan formulation may contain other ingredients typically found in intranasal formulations, such as antioxidants for example sodium metabisulphite, taste-masking agents such as menthol and sweetening agents for example dextrose, glycerol, saccharin and sorbitol.

In another aspect the present invention provides an aqueous solution of zolmitriptan in a buffer at a pH of less than 7.0 in particular at a pH below 6.0, for example in the range 3.5 to 5.5 and in particular in the range 4.5 to 5.5, for example at about 5.0. In particular the present invention provides an aqueous solution of zolmitriptan in a buffer of citric acid and phosphate at a pH of less than 7.0, in particular at a pH below 6.0, for example in the range 3.5 to 5.5 and in particular in the range 4.5 to 5.5, for example at about 5.0.

The pharmaceutical formulation of the present invention may be co-administered (simultaneously or sequentially) with one or more pharmaceutical agents of value in treating migraine or related disease conditions.

The pharmaceutical formulations of the invention will normally be administered to humans so that, for example a unit dose of about 0.5 mg to 15 mg (for example 0.5 mg, 1.0 mg, 2.5 mg, 5.0 mg and 10mg) of zolmitriptan is delivered to the patient in need thereof. The concentration and volume of the formulation may vary as known in the intranasal art, typically a volume of 50 to 250µl is administered, for example 50µl or 100µl (in one spray or in two 50µl sprays - one for each nostril), The precise dose delivered depends on various factors known in the art including the weight, age and sex of the patient being treated and on the particular migraine disease condition being treated. Such a unit dose may be taken at any stage in the onset of, or during the course of, a migraine attack. Such a unit dose may be taken as needed, typically from 1 to 3 times a day.

The pharmaceutical formulations of this invention may be prepared by dissolving zolmitriptan in an acidic medium, for example aqueous citric acid, thereby forming the citrate salt of zolmitriptan, and taking the pH to the desired value by adding a suitable agent for example a phosphate. The resultant buffered solution is typically manufactured to ensure that it contains a low bioburden or to ensure that it is sterile. Typically the solution is sterilised for example by passing through a sterile filter (for example 0.2 µm) or by autoclaving. Preferably, the solution is purged with nitrogen, and overlaid with nitrogen in the primary pack, to minimise the possibility of degradation. Alternatively, another inert gas, such as argon, could be used. Therefore in another aspect the present invention provides a sterile

pharmaceutical formulation suitable for intranasal administration which comprises zolmitriptan and a pharmaceutically acceptable carrier wherein the pH of the formulation is less than 7.0.

The pharmaceutical formulations of the invention are typically filled into a suitable administration device capable of delivering a unit dose amount of zolmitriptan to the patient in need thereof. Such administration devices include those available commercially and the device disclosed in UK Registered Design 2071555. Therefore in a another aspect, the present invention provides an intranasal administration device containing zolmitriptan and a pharmaceutically acceptable carrier wherein the pH of the formulation is less than 7.0.

The filled intranasal administration device may be packaged to provide protection from light. Accordingly in yet a further aspect, the present invention provides an intranasal administration device containing zolmitriptan and a pharmaceutically acceptable carrier in light-protecting packaging, for example in foil pouches. In an alternative aspect, the device itself is a dark colour to provide protection from light, for example, a dark blue colour.

Therefore in a further aspect the present invention provides a pharmaceutical formulation suitable for intranasal administration which comprises zolmitriptan and a pharmaceutically acceptable carrier wherein the pH of the formulation is less than 7.0 for use in a method of therapeutic treatment of the human or animal body.

In yet a further aspect the present invention provides a method of treating a disease condition wherein agonism of 5HT1-receptors is beneficial which comprises administering an effective amount of a pharmaceutical formulation suitable for intranasal administration which comprises zolmitriptan and a pharmaceutically acceptable carrier wherein the pH of the formulation is less than 7.0. The present invention also provides the use of zolmitriptan and a pharmaceutically acceptable carrier in the manufacture of a pharmaceutical formulation suitable for intranasal administration wherein the pH of the formulation is less than 7.0.

Zolmitriptan used in the formulations of the present invention may be prepared according to the disclosures of WO 91/18897 and WO 97/06162.

Examples 1-4

Zolmitriptan is dissolved in an aqueous solution of citric acid, 0.4M disodium phosphate dodecahydrate is added to pH 5.0 and water of injection is added to the desired volume. In this manner solutions with concentrations of zolmitriptan of 5 mg/mL, 10

mg/mL, 25 mg/mL and 50 mg/mL are prepared. The solution is filtered through a sterilizing grade filter (0.2 μm), and filled into USP/Ph Eur Type 1 glass vials (nominal spray volume 100μL) which are closed with chlorobutyl stoppers.

Table 1

Nasal Spray Nominal Strength	0.5 mg	1 mg	2.5 mg	5 mg
Solution Concentration	5 mg/ml	10 mg/ml	25 mg/ml	50 mg/ml
Zolmitriptan	0.5	1.0	2.5	5.0
Citric acid, anhydrous USP/Ph Eur	1.11	1.29	1.79	2.60
Disodium phosphate dodecahydrate USP/Ph Eur*	qs to pH 5.0	qs to pH 5.0	qs to pH 5.0	qs to pH 5.0
Water for Injections USP/Ph Eur	to 0.1 ml	to 0.1 ml	to 0.1 ml	to 0.1 ml

* Added as a 0.4 M solution of Disodium Phosphate Dodecahydrate Ph Eur/USP diluted with purified water USP/Ph Eur.

The vials are assembled into the unit dose nasal spray device disclosed in UK Registered Design 2071555. This device comprises a vial holder, an actuation device and a protection cap. The assembled device may be used to deliver unit doses of zolmitriptan of 0.5 mg, 1.0 mg, 2.5 mg or 5.0 mg in a single administration. The filled nasal spray device is packaged into a plastic tray and placed inside a carton to provide protection from the light.

Examples 5-8

Zolmitriptan is dissolved in an aqueous solution of citric acid, 0.4M disodium phosphate is added to pH 5.0 and water of injection is added to the desired volume. In this manner solutions with concentrations of zolmitriptan of 5 mg/mL, 10 mg/mL, 25 mg/mL and 50 mg/mL are prepared. The solution is filtered and filled into USP/Ph Eur Type 1 glass vials (nominal spray volume 100µL) which are closed with chlorobutyl stoppers.

Table 1

Nasal Spray Nominal Strength	0.5 mg	1 mg	2.5 mg	5 mg
Solution Concentration	5 mg/ml	10 mg/ml	25 mg/ml	50 mg/ml
Zolmitriptan	0.5	1.0	2.5	5.0
Citric acid, anhydrous USP/Ph Eur	1.11	1.29	1.79	2.60
Disodium phosphate USP/Ph Eur*	qs to pH 5.0	qs to pH 5.0	qs to pH 5.0	qs to pH 5.0
Purified Water USP/Ph Eur	to 0.1 ml	to 0.1 ml	to 0.1 ml	to 0.1 ml

* Added as a 0.4 M solution of Disodium Phosphate Ph Eur/USP diluted with purified water for injection.

The vials are autoclaved at 121°C for 15 minutes. They are then assembled into the unit dose nasal spray device disclosed in UK Registered Design 2071555. This device comprises a vial holder, an actuation device and a protection cap. The assembled device may be used to deliver unit doses of zolmitriptan of 0.5 mg, 1.0 mg, 2.5 mg or 5.0 mg in a single administration. The filled nasal spray device is packaged into a plastic tray and placed inside a carton to provide protection from the light.

Example 9

The patient removes the packaging from the nasal spray device, and then removes the protection cap. The patient then inserts the nozzle of the device into a nostril and actuates it to administer a single dose.

CLAIMS

1. A pharmaceutical formulation suitable for intranasal administration which comprises zolmitriptan and a pharmaceutically acceptable carrier wherein the pH of the formulation is less than 7.0.

2. A pharmaceutical formulation according to claim 1 wherein the pH of the formulation is in the range 4.5 to 5.5.

3. A pharmaceutical formulation according to either claim 1 or claim 2 wherein the formulation is buffered.

4. A pharmaceutical formulation according to claim 3 wherein the buffer is a mixture of citric acid and disodium phosphate.

5. A pharmaceutical formulation according to any one of claims 1 to 4 which is sterile.

6. A process for preparing a sterile pharmaceutical formulation as defined in claim 5 which comprises autoclaving.

7. A method of treating a disease condition wherein agonism of 5HT1-receptors is beneficial which comprises administering an effective amount of a pharmaceutical formulation as defined in any one of claims 1 to 5.

8. The use of zolmitriptan in the manufacture of a pharmaceutical formulation as defined in any one of claims 1 to 5.

9. An intranasal administration device containing a pharmaceutical formulation as defined in any one of claims 1 to 5.

10. An intranasal administration device containing a pharmaceutical formulation as defined in any one of claims 1 to 5 when packaged to provide protection from light.

11. An aqueous solution of zolmitriptan in a buffer at a pH of less than 7.0.

12. An aqueous solution of zolmitriptan in a buffer at a pH in the range 4.5 to 5.5

13. A citrate salt of zolmitriptan.

14. A citrate salt of zolmitriptan in aqueous solution.

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(19) World Intellectual Property Organization
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(74) Agent: DENERLEY, Paul, Millington; AstraZeneca, Global Intellectual Property, P.O. Box 272, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4GR (GB).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

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WO 01/39772 A1

(54) Title: PHARMACEUTICAL FORMULATIONS CONTAINING ZOLMITRIPTAN

(57) Abstract: A pharmaceutical formulation of the 5HT1-agonist, zolmitriptan, for use in intranasal administration. The formulation is useful in treating migraine and related disorders.

10129973-092317-1PUS
2-20617-1PUS

DECLARATION FOR UTILITY PATENT APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

PHARMACEUTICAL FORMULATIONS CONTAINING ZOLMITRIPTAN

a patent application , the specification of which (check one)

☒ is attached hereto.
☐ was filed on _____, as United States Application Number _____ and was amended on (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information, which is material to patentability as defined in Title 37, Code of Federal Regulation, § 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, § 119(a)-(d) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)			Priority Claimed
9928578.5 (Number)	United Kingdom (Country)	December 3, 1999 (Day/Month/Year Filed)	☒ Yes ☐ No

I hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States Provisional application(s) listed below.

(Application Number)	(Filing Date)

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

(Application Number)	(Filing Date)	(Status: patented, pending, abandoned)
PCT/GB00/04528	November 28, 2000	Pending

I hereby appoint Madeline F. Baer, Reg. No. 36,437; J. Steven Baughman, Reg. No. 47,414; Johnny Y. Chen, Reg. No. 46,614; Gregory G. Glover, Reg. No. 34,173; William G. Gosz, Reg. No.: 27,787, Patricia Granahan, Reg. No. 32,227; David P. Halstead, Reg. No. 44,735; Daniel Hansburg, Reg. No. 36,156; Edward J. Kelly, Reg. No. 38,936; Charles Larsen, Reg. No. 48,533; Agnes S. Lee, Reg. No. 46,862; Paul E. Lewkowicz, Reg. No. 44,870; Yu Lu, Reg. No. P-50,306; Christopher T. Natkanski, Reg. No. P-50,365; Robert A. Mazzarese, Reg. No. 42,852; Spencer Schneider, Reg. No. 45,923; Sanjay Sitlani, Reg. No. 48,489; Wolfgang Stutius, Reg. No. 40,256; Matthew P. Vincent, Reg. No. 36,709; as attorneys/agents to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith.

Address all telephone calls to Patricia Granahan at telephone number (617) 951-7449.

Address all correspondence to: **Customer Id No: 28120**

Docketing Specialist 33/48
Ropes & Gray LLP
One International Place
Boston, Ma. 02110-2624

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole or first inventor (given name, family name): ALAN ROY DEARN
Inventor's signature: _____ Date: 23 April 2002
Residence: Park Road, Ware, Hertfordshire SG12 0DP, United Kingdom Citizenship: United Kingdom
Post Office Address: _____

Full name of second inventor (given name, family name): **SARAH LOUISE WILLIAMSON**
Inventor's signature: S Williamson Date: 25 APR 2002
Residence: Park Road, Ware, Hertfordshire SG12 0DP, United Kingdom GBX Citizenship: United Kingdom
Post Office Address:

3-00

Full name of third inventor (given name, family name): **SIMON JOHN SUMMERS**
Inventor's signature: S Summers Date: 25th April 2002
Residence: Park Road, Ware, Hertfordshire SG12 0DP, United Kingdom GBX Citizenship: United Kingdom
Post Office Address:

4-00

Full name of fourth inventor (given name, family name): **TREVOR JOHN COOMBER**
Inventor's signature: T J Coomber Date: 26th April 2002
Residence: Park Road, Ware, Hertfordshire SG12 0DP, United Kingdom GBX Citizenship: United Kingdom
Post Office Address:

DECLARATION FOR UTILITY PATENT APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

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a patent application , the specification of which (check one)

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☐ was filed on _____, as United States Application Number _____ and was amended on (if applicable).

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One International Place
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Inventor's signature: _____
Date: 23 April 2002
Residence: Park Road, Ware, Hertfordshire SG12 0DP, United Kingdom
Citizenship: United Kingdom
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Full name of second inventor (given name, family name): SARAH LOUISE WILLIAMSON
Inventor's signature: Sarah Williamson Date: 25 APR 2002
Residence: Park Road, Ware, Hertfordshire SG12 0DP, United Kingdom GBX Citizenship: United Kingdom
Post Office Address:

3-00

Full name of third inventor (given name, family name): SIMON JOHN SUMMERS
Inventor's signature: Date: 25th April 2002
Residence: Park Road, Ware, Hertfordshire SG12 0DP, United Kingdom GBX Citizenship: United Kingdom
Post Office Address:

4-00

Full name of fourth inventor (given name, family name): TREVOR JOHN COOMBER
Inventor's signature: T J Coomber Date: 26th April 2002
Residence: Park Road, Ware, Hertfordshire SG12 0DP, United Kingdom GBX Citizenship: United Kingdom
Post Office Address:

I hereby certify that this correspondence is being deposited with the U.S. Postal Service with sufficient postage as First Class Mail, in an envelope addressed to: Box PCT, Commissioner for Patents, Washington, DC 20231, on the date shown below.

Dated: August 21, 2002 Signature: (Brent LaBarge)

DT83 Rec'd PCT/PTO 28 AUG 2002

Docket No.: ASZD-P01-617
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Dearn et al.

Application No.: 10/129773

Group Art Unit: N/A

Filed: May 9, 2002

Examiner: Not Yet Assigned

For: Pharmaceutical Formulations Containing Zolmitriptan

RESPONSE TO NOTICE TO FILE MISSING PARTS OF APPLICATION

Box PCT
Commissioner for Patents
Washington, DC 20231

Dear Sir:

In response to the Notification of Missing Requirements mailed July 29, 2002, Applicants respectfully submit a Combined Declaration and Power of Attorney.

Please charge our Deposit Account No. 18-1945 in the amount of $130.00 covering the fee set forth in 37 CFR 1.16(e). The Commissioner is hereby authorized to credit any overpayment or charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 18-1945, under Order No. ASZD-P01-617. A duplicate copy of this paper is enclosed.

Dated: August 21, 2002

Respectfully submitted,

By _____
David P. Halstead, Ph.D.
Registration No.: 44,735
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08/30/2002 SNAJARRO 00000153 181945 10129773
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FEE TRANSMITTAL for FY 2002

Patent fees are subject to annual revision.

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 130.00

Complete if Known	
Application Number	10/129773
Filing Date	May 9, 2002
First Named Inventor	Alan Roy Dearn
Examiner Name	Not Yet Assigned
Group Art Unit	N/A
Attorney Docket No.	ASZD-P01-617

METHOD OF PAYMENT *(check all that apply)*

☐ Check ☐ Credit Card ☐ Money Order ☐ Other ☐ None

☒ Deposit Account

Deposit Account Number: 18-1945

Deposit Account Name: Ropes & Gray

The Commissioner is hereby authorized to: *(check all that apply)*

☒ Charge fee(s) indicated below ☒ Credit any overpayments

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☐ Charge fee(s) indicated below, **except for the filing fee**

to the above-identified deposit account.

FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
101	740	201	370	Utility filing fee	
106	330	206	165	Design filing fee	
107	510	207	255	Plant filing fee	
108	740	208	370	Reissue filing fee	
114	160	214	80	Provisional filing fee	

SUBTOTAL (1) ($) 0.00

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

			Extra Claims	Fee from below	Fee Paid
Total Claims	57	-57** =		x =	0.00
Independent Claims	5	-5** =		x =	0.00
Multiple Dependent				=	

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
103	18	203	9	Claims in excess of 20
102	84	202	42	Independent claims in excess of 3
104	280	204	140	Multiple dependent claim, if not paid
109	84	209	42	** Reissue independent claims over original patent
110	18	210	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($) 0.00

***or number previously paid, if greater; For Reissues, see above*

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
105	130	205	65	Surcharge – late filing fee or oath	130.00
127	50	227	25	Surcharge – late provisional filing fee or cover sheet.	
139	130	139	130	Non-English specification	
147	2,520	147	2,520	For filing a request for *ex parte* reexamination	
112	920*	112	920*	Requesting publication of SIR prior to Examiner action	
113	1,840*	113	1,840*	Requesting publication of SIR after Examiner action	
115	110	215	55	Extension for reply within first month	
116	400	216	200	Extension for reply within second month	
117	920	217	460	Extension for reply within third month	
118	1,440	218	720	Extension for reply within fourth month	
128	1,960	228	980	Extension for reply within fifth month	
119	320	219	160	Notice of Appeal	
120	320	220	160	Filing a brief in support of an appeal	
121	280	221	140	Request for oral hearing	
138	1,510	138	1,510	Petition to institute a public use proceeding	
140	110	240	55	Petition to revive – unavoidable	
141	1,280	241	640	Petition to revive - unintentional	
142	1,280	242	640	Utility issue fee (or reissue)	
143	460	243	230	Design issue fee	
144	620	244	310	Plant issue fee	
122	130	122	130	Petitions to the Commissioner	
123	50	123	50	Processing fee under 37 CFR 1.17(q)	
126	180	126	180	Submission of Information Disclosure Stmt	
581	40	581	40	Recording each patent assignment per property (times number of properties)	
146	740	246	370	Filing a submission after final rejection (37 CFR 1.129(a))	
149	740	249	370	For each additional invention to be examined (37CFR 1.129(b))	
179	740	279	370	Request for Continued Examination (RCE)	
169	900	169	900	Request for expedited examination of a design application	
Other fee (specify)					

*Reduced by Basic Filing Fee Paid

SUBTOTAL (3) ($) 130.00

SUBMITTED BY				Complete *(if applicable)*	
Name (Print/Type)	David P. Halstead, Ph.D.	*Registration No. (Attorney/Agent)*	44,735	*Telephone*	(617) 951-7615
Signature				*Date*	August 21, 2002

I hereby certify that this correspondence is being deposited with the U.S. Postal Service with sufficient postage as First Class Mail, in an envelope addressed to: Commissioner for Patents, Washington, DC 20231, on the date shown below.

Dated: August 21, 2002 Signature: _____ (Brent LaBarge)

8886937

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents, Box PCT
United States Patent and Trademark Office
Washington, D.C. 20231
www.uspto.gov

U.S. APPLICATION NUMBER NO.	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
10/129,773	Dearn	ASZD-P01-617

INTERNATIONAL APPLICATION NO.	
PCT/GB00/04528	
I.A. FILING DATE	PRIORITY DATE
11/28/2000	12/03/1999

David P Halstead
Ropes & Gray
One International Place
Boston, MA 02110-2624

CONFIRMATION NO. 7672

371 FORMALITIES LETTER

OC000000008523984

Date Mailed: 07/29/2002

NOTIFICATION OF MISSING REQUIREMENTS UNDER 35 U.S.C. 371 IN THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US)

The following items have been submitted by the applicant or the IB to the United States Patent and Trademark Office as an Elected Office (37 CFR 1.495):

- U.S. Basic National Fees
- Priority Document
- Copy of IPE Report
- Copy of references cited in ISR
- Copy of the International Application
- Copy of the International Search Report
- Information Disclosure Statements
- Oath or Declaration
- Substitute Specification

R&G
Docket No.: ASZD-P01-617
Action: MP - Oath Fee
Stat. Deadline: 29Sept02/28Feb02

The following items **MUST** be furnished within the period set forth below in order to complete the requirements for acceptance under 35 U.S.C. 371:

- Oath or declaration of the inventors, in compliance with 37 CFR 1.497(a) and (b), identifying the application by the International application number and international filing date. The current oath or declaration does not comply with 37 CFR 1.497(a) and (b) in that it:
  - is not executed in accordance with either 37 CFR 1.66 or 37 CFR 1.68.

- **$130** Surcharge for providing the oath or declaration later than the appropriate 30 months months from the priority date (37 CFR 1.492(e)) is required.

ALL OF THE ITEMS SET FORTH ABOVE MUST BE SUBMITTED WITHIN TWO (2) MONTH FROM THE DATE OF THIS NOTICE OR BY 22 or 32 MONTHS (where 37 CFR 1.495 applies) FROM THE PRIORITY DATE FOR THE APPLICATION, WHICHEVER IS LATER. FAILURE TO PROPERLY RESPOND WILL RESULT IN ABANDONMENT.

The time period set above may be extended by filing a petition and fee for extension of time under the provisions of 37 CFR 1.136(a).

SUMMARY OF FEES DUE:

Total additional fees required for this application is **$130** for a Large Entity:

- **$130** Late oath or declaration Surcharge.

Applicant is reminded that any communications to the United States Patent and Trademark Office must be mailed to the address given in the heading and include the U.S. application no. shown above (37 CFR 1.5)

*A copy of this notice **MUST** be returned with the response.*

PAULETTE R KIDWELL

Telephone: (703) 305-3656

PART 1 - ATTORNEY/APPLICANT COPY

U.S. APPLICATION NUMBER NO.	INTERNATIONAL APPLICATION NO.	ATTY. DOCKET NO.
10/129,773	PCT/GB00/04528	ASZD-P01-617

FORM PCT/DO/EO/905 (371 Formalities Notice)

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents, Box PCT
United States Patent and Trademark Office
Washington, D.C. 20231
www.uspto.gov

U.S. APPLICATION NUMBER NO.	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
10/129,773	Dearn	ASZD-P01-617

INTERNATIONAL APPLICATION NO.	
PCT/GB00/04528	
I.A. FILING DATE	PRIORITY DATE
11/28/2000	12/03/1999

David P Halstead
Ropes & Gray
One International Place
Boston, MA 02110-2624

CONFIRMATION NO. 7672

371 FORMALITIES LETTER

OC000000008523984

Date Mailed: 07/29/2002

NOTIFICATION OF MISSING REQUIREMENTS UNDER 35 U.S.C. 371 IN THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US)

The following items have been submitted by the applicant or the IB to the United States Patent and Trademark Office as an Elected Office (37 CFR 1.495):

- U.S. Basic National Fees
- Priority Document
- Copy of IPE Report
- Copy of references cited in ISR
- Copy of the International Application
- Copy of the International Search Report
- Information Disclosure Statements
- Oath or Declaration
- Substitute Specification

The following items **MUST** be furnished within the period set forth below in order to complete the requirements for acceptance under 35 U.S.C. 371:

- Oath or declaration of the inventors, in compliance with 37 CFR 1.497(a) and (b), identifying the application by the International application number and international filing date. The current oath or declaration does not comply with 37 CFR 1.497(a) and (b) in that it:
  - is not executed in accordance with either 37 CFR 1.66 or 37 CFR 1.68.

- **$130** Surcharge for providing the oath or declaration later than the appropriate 30 months months from the priority date (37 CFR 1.492(e)) is required.

ALL OF THE ITEMS SET FORTH ABOVE MUST BE SUBMITTED WITHIN TWO (2) MONTH FROM THE DATE OF THIS NOTICE OR BY 22 or 32 MONTHS (where 37 CFR 1.495 applies) FROM THE PRIORITY DATE FOR THE APPLICATION, WHICHEVER IS LATER. FAILURE TO PROPERLY RESPOND WILL RESULT IN ABANDONMENT.

The time period set above may be extended by filing a petition and fee for extension of time under the provisions of 37 CFR 1.136(a).

SUMMARY OF FEES DUE:

Total additional fees required for this application is **$130** for a Large Entity:

- **$130** Late oath or declaration Surcharge.

Applicant is reminded that any communications to the United States Patent and Trademark Office must be mailed to the address given in the heading and include the U.S. application no. shown above (37 CFR 1.5)

*A copy of this notice **MUST** be returned with the response.*

PAULETTE R KIDWELL

Telephone: (703) 305-3656

PART 2 - OFFICE COPY

U.S. APPLICATION NUMBER NO.	INTERNATIONAL APPLICATION NO.	ATTY. DOCKET NO.
10/129,773	PCT/GB00/04528	ASZD-P01-617

FORM PCT/DO/EO/905 (371 Formalities Notice)

10/129773

FILED UNDER 35 U.S.C. 371

PATENT NUMBER and ISSUE DATE

U.S. UTILITY Patent Application

APPL NUM	FILING DATE	CLASS	SUBCLASS	GAU	EXAMINER
10129773	08/28/2002	514	378	~~1614~~ 1626	PRYOR

3/19/03

**APPLICANTS: Dearn Alan; Williamson Sarah; Summers Simon; Coomber Trevor;

**CONTINUING DATA VERIFIED:

This application is a 371 of PCT/GB00/04528 11/28/2000

** FOREIGN APPLICATIONS VERIFIED:

UNITED KINGDOM 9928578.5 12/03/1999

PG-PUB	DO NOT PUBLISH ☐	RESCIND ☐
Foreign priority claimed	☒ yes ☐ no	ATTORNEY DOCKET NO
35 USC 119 conditions met	☒ yes ☐ no	ASZD-P01-617
Verified and Acknowledged Examiners's intials		

TITLE : Pharmaceutical formulations containing zolmitriptan

U.S.DEPT. OF COMM /PAT & TM-PTO-436L(Rev. 12-94)

NOTICE OF ALLOWANCE MAILED	Assistant Examiner	CLAIMS ALLOWED	
		Total Claims	Print Claim for O.G
ISSUE FEE		DRAWING	
Amount Due / Date Paid	Primary Examiner	Sheets Drwg. / Figs.Drwg. / Print Fig.	
☐ TERMINAL DISCLAIMER	PREPARED FOR ISSUE	Application Examiner	

FILED WITH: ☐ DISK (CRF) ☐ CD-ROM

(Attached in pocket on right inside flap)

SEARCH

Class	Sub.	Date	Exmr.
514	376	~~8/12/03~~	DMP
548	122	8/14/03	DMP

SEARCH NOTES

(List databases searched. Attach search strategy inside.)

	Date	Exmr.
SCW/ WEST	8/14/03	DMP

INTERFERENCE SEARCHED

Class	Sub.	Date	Exmr.

ISSUE SLIP STAPLE AREA (for additional cross-references)

ISSUING CLASSIFICATION

ORIGINAL		CROSS REFERENCE(S)	
CLASS	SUBCLASS	CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)
INTERNATIONAL CLASSIFICATION			
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INDEX OF CLAIMS

✓ ..... Rejected - (Through numeral) ... Canceled N ..... Non-elected A ..... Appeal
= ..... Allowed + ... Restricted I ..... Interference O ..... Objected

Claim		Date
Final	Original	
	1	✓
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If more than 150 claims or 9 actions stapl additional sheet h r

JC02 Rec'd PCT/PTO 09 MAY 2002

FORM PTO 1390 (REV 9-2001) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		ATTORNEY'S DOCKET NUMBER
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		ASZD-P01-617
		U.S. APPLICATION NO. (If known, see 37 CFR 1.5) 10/129773
INTERNATIONAL APPLICATION NO. PCT/GB00/04528	INTERNATIONAL FILING DATES 28/11/2000	PRIORITY DATE CLAIMED 3/12/1999

TITLE OF INVENTION PHARMACEUTICAL FORMULATIONS CONTAINING ZOLMITRIPTAN

APPLICANT(S) FOR DO/EO/US Deam et al.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [x] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing 35 U.S.C. 371
3. [ ] This is an express request to begin national examination procedures (35 U.S.C. 371 (f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. [x] The US has been elected by the expiration of 19 months from the priority date (PCT Article 31).
5. [x] A copy of the International Application as filed (35 U.S.C. 371 (c)(2))
   a. [ ] is attached hereto (required only if not communicated by the International Bureau).
   b. [x] has been communicated by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [ ] An English language translation of the International Application as filed (35 U.S.C. 371 (c)(2)).
   a. [ ] is attached hereto.
   b. [ ] has been previously submitted under 35 U.S.C. 154(d)(4).
7. [x] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. [ ] are attached hereto (required only if not communicated by the International Bureau).
   b. [ ] have been communicated by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [x] have not been made and will not be made.
8. [ ] An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. [ ] An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. [ ] An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. [x] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [ ] A FIRST preliminary amendment.
14. [ ] A SECOND or SUBSEQUENT preliminary amendment.
15. [x] A substitute specification.
16. [ ] A change of power of attorney and/or address letter.
17. [ ] A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
18. [x] A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. [ ] A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
20. [x] Other items or information: Marked-up Copy of Specification

JC13 Rec'd PCT/PTO 09 MAY 2002

U.S. APPLICATION NO. (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
10/129773	PCT/GB00/04528	ASZD-P01-617

21. [x] The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) – (5)):

		CALCULATIONS PTO USE ONLY
[ ]	Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO $1040.00	
[x]	International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO $890.00	
[ ]	International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO $740.00	
[ ]	International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) $710.00	
[ ]	International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) $100.00	

ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 890.00	
Surcharge of $____ for furnishing the oath or declaration later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).	$	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	57-20 =	37	x 18.00	$ 666.00	
Independent claims	5-3 =	2	x 84.00	$ 168.00	
MULTIPLE DEPENDENT CLAIM(s) (if applicable)			+ 280.00	$ 280.00	
TOTAL OF ABOVE CALCULATIONS =				$ 2,004.00	
[ ] Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by ½.				$	
SUBTOTAL =				$ 2,004.00	
Processing fee of $____ for furnishing the English translation later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492 (f)). +				$	
TOTAL NATIONAL FEE =				$ 2,004.00	
Fee for recording the enclosed assignment (37 CFR 1.21 (h)). Assignment must be accompanied by appropriate cover sheet (37 CFR 3.28, 3.31) + (per property).				$	
TOTAL FEES ENCLOSED =				$ 2,004.00	
				Amount to be Refunded:	$
				Charged:	$

a. [ ] A check in the amount of $ ____ to cover the above fees is enclosed.

b. [x] Please charge my Deposit Account No. 18-1945 in the amount of $ 2,004.00 to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [x] The Commissioner is hereby authorized to charge any additional fees which may be required or credit any overpayment to my Deposit Account No. 18-1945. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

David P. Halstead, Ph.D.
ROPES & GRAY
One International Place
Boston, Massachusetts 02110-2624
(617) 951-7615

SIGNATURE:

David P. Halstead, Ph.D.
NAME

44,735
REGISTRATION NUMBER

SUBSTITUTE SPECIFICATION

PHARMACEUTICAL FORMULATIONS CONTAINING ZOLMITRIPTAN

RELATED APPLICATIONS

This application is a national stage filing under 35 U.S.C. 371 of PCT application PCT/GB00/04528, filed November 28, 2000, which claims priority from Great Britain Application No. 9928578.5, filed December 3, 1999, the specifications of each of which are incorporated by reference herein.

The present invention relates to new pharmaceutical formulations, their preparation and their use in treatment of disease. In particular the present invention relates to pharmaceutical formulations of the anti-migraine drug zolmitriptan for nasal application.

Zolmitriptan has the chemical name (S)-4-{{3-[2-(dimethylaminoethyl]-1H-indol-5-yl]methyl]-2-oxazolidinone. Zolmitriptan is a selective 5HT1-receptor agonist. The 5HT1-receptor mediates vasoconstriction and thus modifies blood flow to the carotid vascular bed. 5HT1-receptor agonists are beneficial in the treatment (including prophylaxis) of disease conditions wherein vasoconstriction in the carotid vascular bed is indicated, for example migraine, cluster headache and headache associated with vascular disorders, hereinafter referred to collectively as 'migraine'. Zolmitriptan has been developed for the acute treatment of migraine in the form of a 2.5 mg and 5 mg tablet intended to be taken up to a maximum of 15 mg per day.

Although zolmitriptan is a successful drug of considerable benefit to migraine sufferers, there is a continuing need for alternative methods for the direct treatment of migraine and the prophylactic treatment of migraine. In particular, patients suffering from migraine or the onset of migraine need fast relief of their suffering.

Zolmitriptan is a member of a class of drugs known as triptans, for example sumatriptan, naratriptan and rizatriptan, which are prescribed for the treatment of migraine. The leader in terms of sales is sumitriptan which has been marketed as an oral formulation. A subcutaneous formulation was also developed; this was more efficacious (P Tfelt-Hansen, Cephalalgia 1998, Vol 18(8), page 532-8) and gave a faster onset of action but was not so acceptable to the patient. An intranasal spray was also developed. This was more user-friendly than the subcutaneous injection but was reported to be less effective in reducing the symptoms of migraine attacks (C Dahlof, Cephalalgia 1998; 18(5): 278-282). Also, many patients reported an unpleasant bitter taste after using the nasal spray.

The present inventors sought a formulation of zolmitriptan that achieved fast relief whilst maintaining high efficacy. They also sought a formulation that, for the wide variety of patients that suffer from migraines, had a more acceptable route of administration than a subcutaneous injection. Clearly, the thought of a subcutaneous injection may dissuade many patients from taking appropriate and necessary treatment. Furthermore, the inventors sought

a formulation that was convenient, effective and acceptable to the patient and did not cause any unnecessary irritancy or side-effects.

USP5466699 discloses a class of chemical compounds for the treatment and prophylaxis of migraine. USP5466699 discloses that this class of compounds may be formulated for oral, sublingual, buccal, parenteral (for example subcutaneous, intramuscular or intraveneous), rectal, topical and intranasal administration and examples of such possible formulations, including an example of an intranasal formulation, are disclosed. The intranasal formulation consists of an active ingredient, methyl hydroxybenzoate (0.2%), propyl hydroxybenzoate (0.02%), citrate buffer and sufficient hydrochloric acid to take the pH to 7.

The present inventors devised an intranasal formulation of zolmitriptan that provided effective and improved fast relief for migraine sufferers. Although, the inventors do not wish to be bound by theory, it is thought that this is at least partly due to the direct mucosal absorption of a significant proportion of zolmitriptan administered by the intranasal route.

Furthermore, studies with an intranasal formulation of zolmitriptan having a pH of above 7.0, at a pH of 7.4, showed the stability of that formulation would not be acceptable over extended periods of time.

The present inventors provided an improved rapid onset of action with a stable intranasal formulation of zolmitriptan having a pH of below 7.0. In addition, this formulation was acceptable to the general patient population and did not cause unnecessary irritancy or side effects.

Accordingly the present inventors provide a pharmaceutical formulation suitable for intranasal administration which comprises zolmitriptan and a pharmaceutically acceptable carrier wherein the pH of the formulation is less than 7.0.

The zolmitriptan formulation for intranasal administration is generally prepared as an aqueous formulation and typically is buffered. Suitable buffering agents include citric acid, phosphates such as disodium phosphate (for example the dodecahydrate, heptahydrate, dihydrate and anhydrous forms) or sodium phosphate and mixtures thereof (for example McIlvaine's buffer which is a mixture of citric acid and disodium phosphate).

In a particular aspect the pH of the pharmaceutical formulation of zolmitriptan is below 6.0, for example in the range 3.5 to 5.5, and in particular in the range 4.5 to 5.5. In a particular aspect the pH of the formulation is about 5.0.

In addition to the buffer, the zolmitriptan formulation may contain other ingredients typically found in intranasal formulations, such as antioxidants for example sodium metabisulphite, taste-masking agents such as menthol and sweetening agents for example dextrose, glycerol, saccharin and sorbitol.

In another aspect the present invention provides an aqueous solution of zolmitriptan in a buffer at a pH of less than 7.0 in particular at a pH below 6.0, for example in the range 3.5 to 5.5 and in particular in the range 4.5 to 5.5, for example at about 5.0. In particular the present invention provides an aqueous solution of zolmitriptan in a buffer of citric acid and phosphate at a pH of less than 7.0, in particular at a pH below 6.0, for example in the range 3.5 to 5.5 and in particular in the range 4.5 to 5.5, for example at about 5.0.

The pharmaceutical formulation of the present invention may be co-administered (simultaneously or sequentially) with one or more pharmaceutical agents of value in treating migraine or related disease conditions.

The pharmaceutical formulations of the invention will normally be administered to humans so that, for example a unit dose of about 0.5 mg to 15 mg (for example 0.5 mg, 1.0 mg, 2.5 mg, 5.0 mg and 10mg) of zolmitriptan is delivered to the patient in need thereof. The concentration and volume of the formulation may vary as known in the intranasal art, typically a volume of 50 to 250µl is administered, for example 50µl or 100µl (in one spray or in two 50µl sprays - one for each nostril), The precise dose delivered depends on various factors known in the art including the weight, age and sex of the patient being treated and on the particular migraine disease condition being treated. Such a unit dose may be taken at any stage in the onset of, or during the course of, a migraine attack. Such a unit dose may be taken as needed, typically from 1 to 3 times a day.

The pharmaceutical formulations of this invention may be prepared by dissolving zolmitriptan in an acidic medium, for example aqueous citric acid, thereby forming the citrate salt of zolmitriptan, and taking the pH to the desired value by adding a suitable agent for example a phosphate. The resultant buffered solution is typically manufactured to ensure that it contains a low bioburden or to ensure that it is sterile. Typically the solution is sterilised for example by passing through a sterile filter (for example 0.2 µm) or by autoclaving. Preferably, the solution is purged with nitrogen, and overlaid with nitrogen in the primary pack, to minimise the possibility of degradation. Alternatively, another inert gas, such as argon, could be used. Therefore in another aspect the present invention provides a sterile

pharmaceutical formulation suitable for intranasal administration which comprises zolmitriptan and a pharmaceutically acceptable carrier wherein the pH of the formulation is less than 7.0.

The pharmaceutical formulations of the invention are typically filled into a suitable administration device capable of delivering a unit dose amount of zolmitriptan to the patient in need thereof. Such administration devices include those available commercially and the device disclosed in UK Registered Design 2071555. Therefore in a another aspect, the present invention provides an intranasal administration device containing zolmitriptan and a pharmaceutically acceptable carrier wherein the pH of the formulation is less than 7.0.

The filled intranasal administration device may be packaged to provide protection from light. Accordingly in yet a further aspect, the present invention provides an intranasal administration device containing zolmitriptan and a pharmaceutically acceptable carrier in light-protecting packaging, for example in foil pouches. In an alternative aspect, the device itself is a dark colour to provide protection from light, for example, a dark blue colour.

Therefore in a further aspect the present invention provides a pharmaceutical formulation suitable for intranasal administration which comprises zolmitriptan and a pharmaceutically acceptable carrier wherein the pH of the formulation is less than 7.0 for use in a method of therapeutic treatment of the human or animal body.

In yet a further aspect the present invention provides a method of treating a disease condition wherein agonism of 5HT1-receptors is beneficial which comprises administering an effective amount of a pharmaceutical formulation suitable for intranasal administration which comprises zolmitriptan and a pharmaceutically acceptable carrier wherein the pH of the formulation is less than 7.0. The present invention also provides the use of zolmitriptan and a pharmaceutically acceptable carrier in the manufacture of a pharmaceutical formulation suitable for intranasal administration wherein the pH of the formulation is less than 7.0.

Zolmitriptan used in the formulations of the present invention may be prepared according to the disclosures of WO 91/18897 and WO 97/06162.

Examples 1-4

Zolmitriptan is dissolved in an aqueous solution of citric acid, 0.4M disodium phosphate dodecahydrate is added to pH 5.0 and water of injection is added to the desired volume. In this manner solutions with concentrations of zolmitriptan of 5 mg/mL, 10

mg/mL, 25 mg/mL and 50 mg/mL are prepared. The solution is filtered through a sterilizing grade filter (0.2 μm), and filled into USP/Ph Eur Type 1 glass vials (nominal spray volume 100μL) which are closed with chlorobutyl stoppers.

Table 1

Nasal Spray Nominal Strength	0.5 mg	1 mg	2.5 mg	5 mg
Solution Concentration	5 mg/ml	10 mg/ml	25 mg/ml	50 mg/ml
Zolmitriptan	0.5	1.0	2.5	5.0
Citric acid, anhydrous USP/Ph Eur	1.11	1.29	1.79	2.60
Disodium phosphate dodecahydrate USP/Ph Eur*	qs to pH 5.0	qs to pH 5.0	qs to pH 5.0	qs to pH 5.0
Water for Injections USP/Ph Eur	to 0.1 ml	to 0.1 ml	to 0.1 ml	to 0.1 ml

* Added as a 0.4 M solution of Disodium Phosphate Dodecahydrate Ph Eur/USP diluted with purified water USP/Ph Eur.

The vials are assembled into the unit dose nasal spray device disclosed in UK Registered Design 2071555. This device comprises a vial holder, an actuation device and a protection cap. The assembled device may be used to deliver unit doses of zolmitriptan of 0.5 mg, 1.0 mg, 2.5 mg or 5.0 mg in a single administration. The filled nasal spray device is packaged into a plastic tray and placed inside a carton to provide protection from the light.

Examples 5-8

Zolmitriptan is dissolved in an aqueous solution of citric acid, 0.4M disodium phosphate is added to pH 5.0 and water of injection is added to the desired volume. In this manner solutions with concentrations of zolmitriptan of 5 mg/mL, 10 mg/mL, 25 mg/mL and 50 mg/mL are prepared. The solution is filtered and filled into USP/Ph Eur Type 1 glass vials (nominal spray volume 100µL) which are closed with chlorobutyl stoppers.

Table 1

Nasal Spray Nominal Strength	0.5 mg	1 mg	2.5 mg	5 mg
Solution Concentration	5 mg/ml	10 mg/ml	25 mg/ml	50 mg/ml
Zolmitriptan	0.5	1.0	2.5	5.0
Citric acid, anhydrous USP/Ph Eur	1.11	1.29	1.79	2.60
Disodium phosphate USP/Ph Eur*	qs to pH 5.0	qs to pH 5.0	qs to pH 5.0	qs to pH 5.0
Purified Water USP/Ph Eur	to 0.1 ml	to 0.1 ml	to 0.1 ml	to 0.1 ml

* Added as a 0.4 M solution of Disodium Phosphate Ph Eur/USP diluted with purified water for injection.

The vials are autoclaved at 121°C for 15 minutes. They are then assembled into the unit dose nasal spray device disclosed in UK Registered Design 2071555. This device comprises a vial holder, an actuation device and a protection cap. The assembled device may be used to deliver unit doses of zolmitriptan of 0.5 mg, 1.0 mg, 2.5 mg or 5.0 mg in a single administration. The filled nasal spray device is packaged into a plastic tray and placed inside a carton to provide protection from the light.

Example 9

The patient removes the packaging from the nasal spray device, and then removes the protection cap. The patient then inserts the nozzle of the device into a nostril and actuates it to administer a single dose.

CLAIMS

1. A pharmaceutical formulation suitable for intranasal administration which comprises zolmitriptan and a pharmaceutically acceptable carrier wherein the pH of the formulation is less than 7.0.

2. A pharmaceutical formulation according to claim 1 wherein the pH of the formulation is in the range 4.5 to 5.5.

3. A pharmaceutical formulation according to claim 1 wherein the formulation is buffered.

4. A pharmaceutical formulation according to claim 2 wherein the formulation is buffered.

5. A pharmaceutical formulation according to claim 3 wherein the buffer is a mixture of citric acid and disodium phosphate.

6. A pharmaceutical formulation according to claim 4 wherein the buffer is a mixture of citric acid and disodium phosphate.

7. A pharmaceutical formulation according to claim 1 which is sterile.

8. A pharmaceutical formulation according to claim 2 which is sterile.

9. A pharmaceutical formulation according to claim 3 which is sterile.

10. A pharmaceutical formulation according to claim 4 which is sterile.

11. A pharmaceutical formulation according to claim 5 which is sterile.

12. A pharmaceutical formulation according to claim 6 which is sterile.

13. A process for preparing a sterile pharmaceutical formulation as defined in any one of claims 7-12 which comprises autoclaving.

14. A method of treating a disease condition wherein agonism of 5HT1-receptors is beneficial which comprises administering an effective amount of a pharmaceutical formulation as defined in any one of claims 1 to 12.

15. An intranasal administration device containing a pharmaceutical formulation as defined in any one of claims 1 to 12.

16. An intranasal administration device containing a pharmaceutical formulation as defined in any one of claims 1 to 12 when packaged to provide protection from light.

17. An aqueous solution of zolmitriptan in a buffer at a pH less than 7.0.

18. An aqueous solution of zolmitriptan in a buffer at a pH in the range 4.5 to 5.5.

19. A citrate salt of zolmitriptan.

20. A citrate salt of zolmitriptan in aqueous solution.

ABSTRACT

A pharmaceutical formulation of the 5HT1-agonist, zolmitriptan, for use in intranasal administration. The formulation is useful in treating migraine and related disorders.

MARKED-UP SPECIFICATION

PHARMACEUTICAL FORMULATIONS CONTAINING ZOLMITRIPTAN

RELATED APPLICATIONS

This application is a national stage filing under 35 U.S.C. 371 of PCT application PCT/GB00/04528, filed November 28, 2000, which claims priority from Great Britain Application No. 9928578.5, filed December 3, 1999, the specifications of each of which are incorporated by reference herein.

The present invention relates to new pharmaceutical formulations, their preparation and their use in treatment of disease. In particular the present invention relates to pharmaceutical formulations of the anti-migraine drug zolmitriptan for nasal application.

Zolmitriptan has the chemical name (S)-4-{{3-[2-(dimethylaminoethyl]-1H-indol-5-yl]methyl]-2-oxazolidinone. Zolmitriptan is a selective 5HT1-receptor agonist. The 5HT1-receptor mediates vasoconstriction and thus modifies blood flow to the carotid vascular bed. 5HT1-receptor agonists are beneficial in the treatment (including prophylaxis) of disease conditions wherein vasoconstriction in the carotid vascular bed is indicated, for example migraine, cluster headache and headache associated with vascular disorders, hereinafter referred to collectively as 'migraine'. Zolmitriptan has been developed for the acute treatment of migraine in the form of a 2.5 mg and 5 mg tablet intended to be taken up to a maximum of 15 mg per day.

Although zolmitriptan is a successful drug of considerable benefit to migraine sufferers, there is a continuing need for alternative methods for the direct treatment of migraine and the prophylactic treatment of migraine. In particular, patients suffering from migraine or the onset of migraine need fast relief of their suffering.

Zolmitriptan is a member of a class of drugs known as triptans, for example sumatriptan, naratriptan and rizatriptan, which are prescribed for the treatment of migraine. The leader in terms of sales is sumitriptan which has been marketed as an oral formulation. A subcutaneous formulation was also developed; this was more efficacious (P Tfelt-Hansen, Cephalalgia 1998, Vol 18(8), page 532-8) and gave a faster onset of action but was not so acceptable to the patient. An intranasal spray was also developed. This was more user-friendly than the subcutaneous injection but was reported to be less effective in reducing the symptoms of migraine attacks (C Dahlof, Cephalalgia 1998; 18(5): 278-282). Also, many patients reported an unpleasant bitter taste after using the nasal spray.

The present inventors sought a formulation of zolmitriptan that achieved fast relief whilst maintaining high efficacy. They also sought a formulation that, for the wide variety of patients that suffer from migraines, had a more acceptable route of administration than a subcutaneous injection. Clearly, the thought of a subcutaneous injection may dissuade many patients from taking appropriate and necessary treatment. Furthermore, the inventors sought

a formulation that was convenient, effective and acceptable to the patient and did not cause any unnecessary irritancy or side-effects.

USP5466699 discloses a class of chemical compounds for the treatment and prophylaxis of migraine. USP5466699 discloses that this class of compounds may be formulated for oral, sublingual, buccal, parenteral (for example subcutaneous, intramuscular or intraveneous), rectal, topical and intranasal administration and examples of such possible formulations, including an example of an intranasal formulation, are disclosed. The intranasal formulation consists of an active ingredient, methyl hydroxybenzoate (0.2%), propyl hydroxybenzoate (0.02%), citrate buffer and sufficient hydrochloric acid to take the pH to 7.

The present inventors devised an intranasal formulation of zolmitriptan that provided effective and improved fast relief for migraine sufferers. Although, the inventors do not wish to be bound by theory, it is thought that this is at least partly due to the direct mucosal absorption of a significant proportion of zolmitriptan administered by the intranasal route.

Furthermore, studies with an intranasal formulation of zolmitriptan having a pH of above 7.0, at a pH of 7.4, showed the stability of that formulation would not be acceptable over extended periods of time.

The present inventors provided an improved rapid onset of action with a stable intranasal formulation of zolmitriptan having a pH of below 7.0. In addition, this formulation was acceptable to the general patient population and did not cause unnecessary irritancy or side effects.

Accordingly the present inventors provide a pharmaceutical formulation suitable for intranasal administration which comprises zolmitriptan and a pharmaceutically acceptable carrier wherein the pH of the formulation is less than 7.0.

The zolmitriptan formulation for intranasal administration is generally prepared as an aqueous formulation and typically is buffered. Suitable buffering agents include citric acid, phosphates such as disodium phosphate (for example the dodecahydrate, heptahydrate, dihydrate and anhydrous forms) or sodium phosphate and mixtures thereof (for example McIlvaine's buffer which is a mixture of citric acid and disodium phosphate).

In a particular aspect the pH of the pharmaceutical formulation of zolmitriptan is below 6.0, for example in the range 3.5 to 5.5, and in particular in the range 4.5 to 5.5. In a particular aspect the pH of the formulation is about 5.0.

In addition to the buffer, the zolmitriptan formulation may contain other ingredients typically found in intranasal formulations, such as antioxidants for example sodium metabisulphite, taste-masking agents such as menthol and sweetening agents for example dextrose, glycerol, saccharin and sorbitol.

In another aspect the present invention provides an aqueous solution of zolmitriptan in a buffer at a pH of less than 7.0 in particular at a pH below 6.0, for example in the range 3.5 to 5.5 and in particular in the range 4.5 to 5.5, for example at about 5.0. In particular the present invention provides an aqueous solution of zolmitriptan in a buffer of citric acid and phosphate at a pH of less than 7.0, in particular at a pH below 6.0, for example in the range 3.5 to 5.5 and in particular in the range 4.5 to 5.5, for example at about 5.0.

The pharmaceutical formulation of the present invention may be co-administered (simultaneously or sequentially) with one or more pharmaceutical agents of value in treating migraine or related disease conditions.

The pharmaceutical formulations of the invention will normally be administered to humans so that, for example a unit dose of about 0.5 mg to 15 mg (for example 0.5 mg, 1.0 mg, 2.5 mg, 5.0 mg and 10mg) of zolmitriptan is delivered to the patient in need thereof. The concentration and volume of the formulation may vary as known in the intranasal art, typically a volume of 50 to 250µl is administered, for example 50µl or 100µl (in one spray or in two 50µl sprays - one for each nostril), The precise dose delivered depends on various factors known in the art including the weight, age and sex of the patient being treated and on the particular migraine disease condition being treated. Such a unit dose may be taken at any stage in the onset of, or during the course of, a migraine attack. Such a unit dose may be taken as needed, typically from 1 to 3 times a day.

The pharmaceutical formulations of this invention may be prepared by dissolving zolmitriptan in an acidic medium, for example aqueous citric acid, thereby forming the citrate salt of zolmitriptan, and taking the pH to the desired value by adding a suitable agent for example a phosphate. The resultant buffered solution is typically manufactured to ensure that it contains a low bioburden or to ensure that it is sterile. Typically the solution is sterilised for example by passing through a sterile filter (for example 0.2 µm) or by autoclaving. Preferably, the solution is purged with nitrogen, and overlaid with nitrogen in the primary pack, to minimise the possibility of degradation. Alternatively, another inert gas, such as argon, could be used. Therefore in another aspect the present invention provides a sterile

pharmaceutical formulation suitable for intranasal administration which comprises zolmitriptan and a pharmaceutically acceptable carrier wherein the pH of the formulation is less than 7.0.

The pharmaceutical formulations of the invention are typically filled into a suitable administration device capable of delivering a unit dose amount of zolmitriptan to the patient in need thereof. Such administration devices include those available commercially and the device disclosed in UK Registered Design 2071555. Therefore in a another aspect, the present invention provides an intranasal administration device containing zolmitriptan and a pharmaceutically acceptable carrier wherein the pH of the formulation is less than 7.0.

The filled intranasal administration device may be packaged to provide protection from light. Accordingly in yet a further aspect, the present invention provides an intranasal administration device containing zolmitriptan and a pharmaceutically acceptable carrier in light-protecting packaging, for example in foil pouches. In an alternative aspect, the device itself is a dark colour to provide protection from light, for example, a dark blue colour.

Therefore in a further aspect the present invention provides a pharmaceutical formulation suitable for intranasal administration which comprises zolmitriptan and a pharmaceutically acceptable carrier wherein the pH of the formulation is less than 7.0 for use in a method of therapeutic treatment of the human or animal body.

In yet a further aspect the present invention provides a method of treating a disease condition wherein agonism of 5HT1-receptors is beneficial which comprises administering an effective amount of a pharmaceutical formulation suitable for intranasal administration which comprises zolmitriptan and a pharmaceutically acceptable carrier wherein the pH of the formulation is less than 7.0. The present invention also provides the use of zolmitriptan and a pharmaceutically acceptable carrier in the manufacture of a pharmaceutical formulation suitable for intranasal administration wherein the pH of the formulation is less than 7.0.

Zolmitriptan used in the formulations of the present invention may be prepared according to the disclosures of WO 91/18897 and WO 97/06162.

Examples 1-4

Zolmitriptan is dissolved in an aqueous solution of citric acid, 0.4M disodium phosphate dodecahydrate is added to pH 5.0 and water of injection is added to the desired volume. In this manner solutions with concentrations of zolmitriptan of 5 mg/mL, 10

mg/mL, 25 mg/mL and 50 mg/mL are prepared. The solution is filtered through a sterilizing grade filter (0.2 μm), and filled into USP/Ph Eur Type 1 glass vials (nominal spray volume 100μL) which are closed with chlorobutyl stoppers.

Table 1

Nasal Spray Nominal Strength	0.5 mg	1 mg	2.5 mg	5 mg
Solution Concentration	5 mg/ml	10 mg/ml	25 mg/ml	50 mg/ml
Zolmitriptan	0.5	1.0	2.5	5.0
Citric acid, anhydrous USP/Ph Eur	1.11	1.29	1.79	2.60
Disodium phosphate dodecahydrate USP/Ph Eur*	qs to pH 5.0	qs to pH 5.0	qs to pH 5.0	qs to pH 5.0
Water for Injections USP/Ph Eur	to 0.1 ml	to 0.1 ml	to 0.1 ml	to 0.1 ml

* Added as a 0.4 M solution of Disodium Phosphate Dodecahydrate Ph Eur/USP diluted with purified water USP/Ph Eur.

The vials are assembled into the unit dose nasal spray device disclosed in UK Registered Design 2071555. This device comprises a vial holder, an actuation device and a protection cap. The assembled device may be used to deliver unit doses of zolmitriptan of 0.5 mg, 1.0 mg, 2.5 mg or 5.0 mg in a single administration. The filled nasal spray device is packaged into a plastic tray and placed inside a carton to provide protection from the light.

Examples 5-8

Zolmitriptan is dissolved in an aqueous solution of citric acid, 0.4M disodium phosphate is added to pH 5.0 and water of injection is added to the desired volume. In this manner solutions with concentrations of zolmitriptan of 5 mg/mL, 10 mg/mL, 25 mg/mL and 50 mg/mL are prepared. The solution is filtered and filled into USP/Ph Eur Type 1 glass vials (nominal spray volume 100μL) which are closed with chlorobutyl stoppers.

Table 1

Nasal Spray Nominal Strength	0.5 mg	1 mg	2.5 mg	5 mg
Solution Concentration	5 mg/ml	10 mg/ml	25 mg/ml	50 mg/ml
Zolmitriptan	0.5	1.0	2.5	5.0
Citric acid, anhydrous USP/Ph Eur	1.11	1.29	1.79	2.60
Disodium phosphate USP/Ph Eur*	qs to pH 5.0	qs to pH 5.0	qs to pH 5.0	qs to pH 5.0
Purified Water USP/Ph Eur	to 0.1 ml	to 0.1 ml	to 0.1 ml	to 0.1 ml

* Added as a 0.4 M solution of Disodium Phosphate Ph Eur/USP diluted with purified water for injection.

The vials are autoclaved at 121°C for 15 minutes. They are then assembled into the unit dose nasal spray device disclosed in UK Registered Design 2071555. This device comprises a vial holder, an actuation device and a protection cap. The assembled device may be used to deliver unit doses of zolmitriptan of 0.5 mg, 1.0 mg, 2.5 mg or 5.0 mg in a single administration. The filled nasal spray device is packaged into a plastic tray and placed inside a carton to provide protection from the light.

Example 9

The patient removes the packaging from the nasal spray device, and then removes the protection cap. The patient then inserts the nozzle of the device into a nostril and actuates it to administer a single dose.

CLAIMS

1. A pharmaceutical formulation suitable for intranasal administration which comprises zolmitriptan and a pharmaceutically acceptable carrier wherein the pH of the formulation is less than 7.0.

2. A pharmaceutical formulation according to claim 1 wherein the pH of the formulation is in the range 4.5 to 5.5.

3. A pharmaceutical formulation according to ~~either~~ claim 1 ~~or claim 2~~ wherein the formulation is buffered.

4. A pharmaceutical formulation according to claim 2 wherein the formulation is buffered.

~~4~~5. A pharmaceutical formulation according to claim 3 wherein the buffer is a mixture of citric acid and disodium phosphate.

6. A pharmaceutical formulation according to claim 4 wherein the buffer is a mixture of citric acid and disodium phosphate.

~~5~~7. A pharmaceutical formulation according to ~~any one of~~ claims 1 ~~to 4~~ which is sterile.

8. A pharmaceutical formulation according to claim 2 which is sterile.

9. A pharmaceutical formulation according to claim 3 which is sterile.

10. A pharmaceutical formulation according to claim 4 which is sterile.

11. A pharmaceutical formulation according to claim 5 which is sterile.

12. A pharmaceutical formulation according to claim 6 which is sterile.

~~6~~13. A process for preparing a sterile pharmaceutical formulation as defined in any one of claims ~~5~~7-12 which comprises autoclaving.

~~7~~14. A method of treating a disease condition wherein agonism of 5HT1-receptors is beneficial which comprises administering an effective amount of a pharmaceutical formulation as defined in any one of claims 1 to ~~5~~12.

~~8. The use of zolmitriptan in the manufacture of a pharmaceutical formulation as defined in any one of claims 1 to 5.~~

~~9~~15. An intranasal administration device containing a pharmaceutical formulation as defined in any one of claims 1 to ~~5~~12.

~~10~~16. An intranasal administration device containing a pharmaceutical formulation as defined in any one of claims 1 to ~~5~~12 when packaged to provide protection from light.

~~11~~17. An aqueous solution of zolmitriptan in a buffer at a pH less than 7.0.

~~12~~18. An aqueous solution of zolmitriptan in a buffer at a pH in the range 4.5 to 5.5.

~~13~~19. A citrate salt of zolmitriptan.

~~14~~20. A citrate salt of zolmitriptan in aqueous solution.

ABSTRACT

A pharmaceutical formulation of the 5HT1-agonist, zolmitriptan, for use in intranasal administration. The formulation is useful in treating migraine and related disorders.

ORIGINAL SPECIFICATION

PHARMACEUTICAL FORMULATIONS CONTAINING ZOLMITRIPTAN

The present invention relates to new pharmaceutical formulations, their preparation and their use in treatment of disease. In particular the present invention relates to pharmaceutical formulations of the anti-migraine drug zolmitriptan for nasal application.

Zolmitriptan has the chemical name (S)-4-{{3-[2-(dimethylaminoethyl]-1H-indol-5-yl]methyl]-2-oxazolidinone. Zolmitriptan is a selective 5HT1-receptor agonist. The 5HT1-receptor mediates vasoconstriction and thus modifies blood flow to the carotid vascular bed. 5HT1-receptor agonists are beneficial in the treatment (including prophylaxis) of disease conditions wherein vasoconstriction in the carotid vascular bed is indicated, for example migraine, cluster headache and headache associated with vascular disorders, hereinafter referred to collectively as 'migraine'. Zolmitriptan has been developed for the acute treatment of migraine in the form of a 2.5 mg and 5 mg tablet intended to be taken up to a maximum of 15 mg per day.

Although zolmitriptan is a successful drug of considerable benefit to migraine sufferers, there is a continuing need for alternative methods for the direct treatment of migraine and the prophylactic treatment of migraine. In particular, patients suffering from migraine or the onset of migraine need fast relief of their suffering.

Zolmitriptan is a member of a class of drugs known as triptans, for example sumatriptan, naratriptan and rizatriptan, which are prescribed for the treatment of migraine. The leader in terms of sales is sumitriptan which has been marketed as an oral formulation. A subcutaneous formulation was also developed; this was more efficacious (P Tfelt-Hansen, Cephalalgia 1998, Vol 18(8), page 532-8) and gave a faster onset of action but was not so acceptable to the patient. An intranasal spray was also developed. This was more user-friendly than the subcutaneous injection but was reported to be less effective in reducing the symptoms of migraine attacks (C Dahlof, Cephalalgia 1998; 18(5): 278-282). Also, many patients reported an unpleasant bitter taste after using the nasal spray.

The present inventors sought a formulation of zolmitriptan that achieved fast relief whilst maintaining high efficacy. They also sought a formulation that, for the wide variety of patients that suffer from migraines, had a more acceptable route of administration than a subcutaneous injection. Clearly, the thought of a subcutaneous injection may dissuade many patients from taking appropriate and necessary treatment. Furthermore, the inventors sought

a formulation that was convenient, effective and acceptable to the patient and did not cause any unnecessary irritancy or side-effects.

USP5466699 discloses a class of chemical compounds for the treatment and prophylaxis of migraine. USP5466699 discloses that this class of compounds may be formulated for oral, sublingual, buccal, parenteral (for example subcutaneous, intramuscular or intraveneous), rectal, topical and intranasal administration and examples of such possible formulations, including an example of an intranasal formulation, are disclosed. The intranasal formulation consists of an active ingredient, methyl hydroxybenzoate (0.2%), propyl hydroxybenzoate (0.02%), citrate buffer and sufficient hydrochloric acid to take the pH to 7.

The present inventors devised an intranasal formulation of zolmitriptan that provided effective and improved fast relief for migraine sufferers. Although, the inventors do not wish to be bound by theory, it is thought that this is at least partly due to the direct mucosal absorption of a significant proportion of zolmitriptan administered by the intranasal route.

Furthermore, studies with an intranasal formulation of zolmitriptan having a pH of above 7.0, at a pH of 7.4, showed the stability of that formulation would not be acceptable over extended periods of time.

The present inventors provided an improved rapid onset of action with a stable intranasal formulation of zolmitriptan having a pH of below 7.0. In addition, this formulation was acceptable to the general patient population and did not cause unnecessary irritancy or side effects.

Accordingly the present inventors provide a pharmaceutical formulation suitable for intranasal administration which comprises zolmitriptan and a pharmaceutically acceptable carrier wherein the pH of the formulation is less than 7.0.

The zolmitriptan formulation for intranasal administration is generally prepared as an aqueous formulation and typically is buffered. Suitable buffering agents include citric acid, phosphates such as disodium phosphate (for example the dodecahydrate, heptahydrate, dihydrate and anhydrous forms) or sodium phosphate and mixtures thereof (for example McIlvaine's buffer which is a mixture of citric acid and disodium phosphate).

In a particular aspect the pH of the pharmaceutical formulation of zolmitriptan is below 6.0, for example in the range 3.5 to 5.5, and in particular in the range 4.5 to 5.5. In a particular aspect the pH of the formulation is about 5.0.

In addition to the buffer, the zolmitriptan formulation may contain other ingredients typically found in intranasal formulations, such as antioxidants for example sodium metabisulphite, taste-masking agents such as menthol and sweetening agents for example dextrose, glycerol, saccharin and sorbitol.

In another aspect the present invention provides an aqueous solution of zolmitriptan in a buffer at a pH of less than 7.0 in particular at a pH below 6.0, for example in the range 3.5 to 5.5 and in particular in the range 4.5 to 5.5, for example at about 5.0. In particular the present invention provides an aqueous solution of zolmitriptan in a buffer of citric acid and phosphate at a pH of less than 7.0, in particular at a pH below 6.0, for example in the range 3.5 to 5.5 and in particular in the range 4.5 to 5.5, for example at about 5.0.

The pharmaceutical formulation of the present invention may be co-administered (simultaneously or sequentially) with one or more pharmaceutical agents of value in treating migraine or related disease conditions.

The pharmaceutical formulations of the invention will normally be administered to humans so that, for example a unit dose of about 0.5 mg to 15 mg (for example 0.5 mg, 1.0 mg, 2.5 mg, 5.0 mg and 10mg) of zolmitriptan is delivered to the patient in need thereof. The concentration and volume of the formulation may vary as known in the intranasal art, typically a volume of 50 to 250µl is administered, for example 50µl or 100µl (in one spray or in two 50µl sprays - one for each nostril), The precise dose delivered depends on various factors known in the art including the weight, age and sex of the patient being treated and on the particular migraine disease condition being treated. Such a unit dose may be taken at any stage in the onset of, or during the course of, a migraine attack. Such a unit dose may be taken as needed, typically from 1 to 3 times a day.

The pharmaceutical formulations of this invention may be prepared by dissolving zolmitriptan in an acidic medium, for example aqueous citric acid, thereby forming the citrate salt of zolmitriptan, and taking the pH to the desired value by adding a suitable agent for example a phosphate. The resultant buffered solution is typically manufactured to ensure that it contains a low bioburden or to ensure that it is sterile. Typically the solution is sterilised for example by passing through a sterile filter (for example 0.2 µm) or by autoclaving. Preferably, the solution is purged with nitrogen, and overlaid with nitrogen in the primary pack, to minimise the possibility of degradation. Alternatively, another inert gas, such as argon, could be used. Therefore in another aspect the present invention provides a sterile

pharmaceutical formulation suitable for intranasal administration which comprises zolmitriptan and a pharmaceutically acceptable carrier wherein the pH of the formulation is less than 7.0.

The pharmaceutical formulations of the invention are typically filled into a suitable administration device capable of delivering a unit dose amount of zolmitriptan to the patient in need thereof. Such administration devices include those available commercially and the device disclosed in UK Registered Design 2071555. Therefore in a another aspect, the present invention provides an intranasal administration device containing zolmitriptan and a pharmaceutically acceptable carrier wherein the pH of the formulation is less than 7.0.

The filled intranasal administration device may be packaged to provide protection from light. Accordingly in yet a further aspect, the present invention provides an intranasal administration device containing zolmitriptan and a pharmaceutically acceptable carrier in light-protecting packaging, for example in foil pouches. In an alternative aspect, the device itself is a dark colour to provide protection from light, for example, a dark blue colour.

Therefore in a further aspect the present invention provides a pharmaceutical formulation suitable for intranasal administration which comprises zolmitriptan and a pharmaceutically acceptable carrier wherein the pH of the formulation is less than 7.0 for use in a method of therapeutic treatment of the human or animal body.

In yet a further aspect the present invention provides a method of treating a disease condition wherein agonism of 5HT1-receptors is beneficial which comprises administering an effective amount of a pharmaceutical formulation suitable for intranasal administration which comprises zolmitriptan and a pharmaceutically acceptable carrier wherein the pH of the formulation is less than 7.0. The present invention also provides the use of zolmitriptan and a pharmaceutically acceptable carrier in the manufacture of a pharmaceutical formulation suitable for intranasal administration wherein the pH of the formulation is less than 7.0.

Zolmitriptan used in the formulations of the present invention may be prepared according to the disclosures of WO 91/18897 and WO 97/06162.

Examples 1-4

Zolmitriptan is dissolved in an aqueous solution of citric acid, 0.4M disodium phosphate dodecahydrate is added to pH 5.0 and water of injection is added to the desired volume. In this manner solutions with concentrations of zolmitriptan of 5 mg/mL, 10

mg/mL, 25 mg/mL and 50 mg/mL are prepared. The solution is filtered through a sterilizing grade filter (0.2 μm), and filled into USP/Ph Eur Type 1 glass vials (nominal spray volume 100μL) which are closed with chlorobutyl stoppers.

Table 1

Nasal Spray Nominal Strength	0.5 mg	1 mg	2.5 mg	5 mg
Solution Concentration	5 mg/ml	10 mg/ml	25 mg/ml	50 mg/ml
Zolmitriptan	0.5	1.0	2.5	5.0
Citric acid, anhydrous USP/Ph Eur	1.11	1.29	1.79	2.60
Disodium phosphate dodecahydrate USP/Ph Eur*	qs to pH 5.0	qs to pH 5.0	qs to pH 5.0	qs to pH 5.0
Water for Injections USP/Ph Eur	to 0.1 ml	to 0.1 ml	to 0.1 ml	to 0.1 ml

* Added as a 0.4 M solution of Disodium Phosphate Dodecahydrate Ph Eur/USP diluted with purified water USP/Ph Eur.

The vials are assembled into the unit dose nasal spray device disclosed in UK Registered Design 2071555. This device comprises a vial holder, an actuation device and a protection cap. The assembled device may be used to deliver unit doses of zolmitriptan of 0.5 mg, 1.0 mg, 2.5 mg or 5.0 mg in a single administration. The filled nasal spray device is packaged into a plastic tray and placed inside a carton to provide protection from the light.

Examples 5-8

Zolmitriptan is dissolved in an aqueous solution of citric acid, 0.4M disodium phosphate is added to pH 5.0 and water of injection is added to the desired volume. In this manner solutions with concentrations of zolmitriptan of 5 mg/mL, 10 mg/mL, 25 mg/mL and 50 mg/mL are prepared. The solution is filtered and filled into USP/Ph Eur Type 1 glass vials (nominal spray volume 100μL) which are closed with chlorobutyl stoppers.

Table 1

Nasal Spray Nominal Strength	0.5 mg	1 mg	2.5 mg	5 mg
Solution Concentration	5 mg/ml	10 mg/ml	25 mg/ml	50 mg/ml
Zolmitriptan	0.5	1.0	2.5	5.0
Citric acid, anhydrous USP/Ph Eur	1.11	1.29	1.79	2.60
Disodium phosphate USP/Ph Eur*	qs to pH 5.0	qs to pH 5.0	qs to pH 5.0	qs to pH 5.0
Purified Water USP/Ph Eur	to 0.1 ml	to 0.1 ml	to 0.1 ml	to 0.1 ml

* Added as a 0.4 M solution of Disodium Phosphate Ph Eur/USP diluted with purified water for injection.

The vials are autoclaved at 121°C for 15 minutes. They are then assembled into the unit dose nasal spray device disclosed in UK Registered Design 2071555. This device comprises a vial holder, an actuation device and a protection cap. The assembled device may be used to deliver unit doses of zolmitriptan of 0.5 mg, 1.0 mg, 2.5 mg or 5.0 mg in a single administration. The filled nasal spray device is packaged into a plastic tray and placed inside a carton to provide protection from the light.

Example 9

The patient removes the packaging from the nasal spray device, and then removes the protection cap. The patient then inserts the nozzle of the device into a nostril and actuates it to administer a single dose.

CLAIMS

1. A pharmaceutical formulation suitable for intranasal administration which comprises zolmitriptan and a pharmaceutically acceptable carrier wherein the pH of the formulation is less than 7.0.

2. A pharmaceutical formulation according to claim 1 wherein the pH of the formulation is in the range 4.5 to 5.5.

3. A pharmaceutical formulation according to either claim 1 or claim 2 wherein the formulation is buffered.

4. A pharmaceutical formulation according to claim 3 wherein the buffer is a mixture of citric acid and disodium phosphate.

5. A pharmaceutical formulation according to any one of claims 1 to 4 which is sterile.

6. A process for preparing a sterile pharmaceutical formulation as defined in claim 5 which comprises autoclaving.

7. A method of treating a disease condition wherein agonism of 5HT1-receptors is beneficial which comprises administering an effective amount of a pharmaceutical formulation as defined in any one of claims 1 to 5.

8. The use of zolmitriptan in the manufacture of a pharmaceutical formulation as defined in any one of claims 1 to 5.

9. An intranasal administration device containing a pharmaceutical formulation as defined in any one of claims 1 to 5.

10. An intranasal administration device containing a pharmaceutical formulation as defined in any one of claims 1 to 5 when packaged to provide protection from light.

11. An aqueous solution of zolmitriptan in a buffer at a pH of less than 7.0.

12. An aqueous solution of zolmitriptan in a buffer at a pH in the range 4.5 to 5.5

13. A citrate salt of zolmitriptan.

14. A citrate salt of zolmitriptan in aqueous solution.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
7 June 2001 (07.06.2001)

PCT

(10) International Publication Number
WO 01/39772 A1

(51) International Patent Classification[7]: A61K 31/4045, 9/00, A61P 25/06

(21) International Application Number: PCT/GB00/04528

(22) International Filing Date:
28 November 2000 (28.11.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
9928578.5 3 December 1999 (03.12.1999) GB

(71) Applicant *(for all designated States except MG, US)*: ASTRAZENECA AB [SE/SE]; S-151 85 Sodertalje (SE).

(71) Applicant *(for MG only)*: ASTRAZENECA UK LIMITED [GB/GB]; 15 Stanhope Gate, London W1Y 6LN (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **DEARN, Alan, Roy** [GB/GB]; Park Road, Ware, Hertfordshire SG12 0DP (GB). **WILLIAMSON, Sarah, Louise** [GB/GB]; Park Road, Ware, Hertfordshire SG12 0DP (GB). **SUMMERS, Simon, John** [GB/GB]; Park Road, Ware, Hertfordshire SG12 0DP (GB). **COOMBER, Trevor, John** [GB/GB]; Park Road, Ware, Hertfordshire SG12 0DP (GB).

(74) Agent: **DENERLEY, Paul, Millington**; AstraZeneca, Global Intellectual Property, P.O. Box 272, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4GR (GB).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*
— *Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/39772 A1

(54) Title: PHARMACEUTICAL FORMULATIONS CONTAINING ZOLMITRIPTAN

(57) Abstract: A pharmaceutical formulation of the 5HT1-agonist, zolmitriptan, for use in intranasal administration. The formulation is useful in treating migraine and related disorders.

DECLARATION FOR UTILITY PATENT APPLICATION

ASZD-P01-617

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

POLYMER-BASED, SUSTAINED RELEASE DRUG DELIVERY SYSTEM

a patent application , the specification of which (check one)

☒ is attached hereto.
☐ was filed on _____, as United States Application Number _____ and was amended on (May 9, 2002).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information, which is material to patentability as defined in Title 37, Code of Federal Regulation, § 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, § 119(a)-(d) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)			Priority Claimed
9928578.5 (Number)	GB (Country)	3 December 1999 (Day/Month/Year Filed)	☒ Yes ☐ No

I hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States Provisional application(s) listed below.

_____ (Application Number) _____ (Filing Date)

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

PCT/GB00/04528 (Application Number)	November 28, 2000 (Filing Date)	Pending (Status: patented, pending, abandoned)
_____ (Application Number)	_____ (Filing Date)	_____ (Status: patented, pending, abandoned)

I hereby appoint Madeline F. Baer, Reg. No. 36,437; J. Steven Baughman, Reg. No. 47,414; Johnny Y. Chen, Reg. No. 46,614; Gregory G. Glover, Reg. No. 34,173; William G. Gosz, Reg. No.: 27,787, Patricia Granahan, Reg. No. 32,227; David P. Halstead, Reg. No. 44,735; Daniel Hansburg, Reg. No. 36,156; Edward J. Kelly, Reg. No. 38,936; Charles Larsen, Reg. No. 48,533; Agnes S. Lee, Reg. No. 46,862; Paul E. Lewkowicz, Reg. No. 44,870; Yu Lu, Reg. No. 50,306; Christopher T. Natkanski, Reg. No. 50,365; Robert A. Mazzarese, Reg. No. 42,852; Spencer Schneider, Reg. No. 45,923; Sanjay Sitlani, Reg. No. 48,489; Wolfgang Stutius, Reg. No. 40,256; Matthew P. Vincent, Reg. No. 36,709; as attorneys/agents to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith.

Address all telephone calls to Patricia Granahan at telephone number (617) 951-7449.

Address all correspondence to: **Customer Id No: 28120**

Docketing Specialist 33/48
Ropes & Gray LLP
One International Place
Boston, Ma. 02110-2624

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole or first inventor (given name, family name): **ALAN ROY DEARN**
Inventor's signature: _____ Date: _____
Residence: Park Road, Ware, Hertfordshire SG12 0DP, United Kingdom Citizenship: United Kingdom
Post Office Address: _____

Full name of second inventor (given name, family name): **SARAH LOUISE WILLIAMSON**
Inventor's signature: _____ Date: _____
Residence: Park Road, Ware, Hertfordshire SG12 0DP, United Kingdom Citizenship: United Kingdom
Post Office Address: _____

Full name of third inventor (given name, family name): **SIMON JOHN SUMMERS**
Inventor's signature: _____ Date: _____
Residence: Park Road, Ware, Hertfordshire SG12 0DP, United Kingdom Citizenship: United Kingdom
Post Office Address: _____

Full name of fourth inventor (given name, family name): **TREVOR JOHN COOMBER**
Inventor's signature: _____ Date: _____
Residence: Park Road, Ware, Hertfordshire SG12 0DP, United Kingdom Citizenship: United Kingdom
Post Office Address: _____

PATENT APPLICATION SERIAL NO. _____

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE
FEE RECORD SHEET

05/21/2002 SNAJARRO 00000040 181945 10129773

01 FC:970 890.00 CH
02 FC:966 ~~666.00 CH~~
03 FC:964 168.00 CH
04 FC:968 280.00 CH

Adjustment date: 07/22/2002 GFREY1
05/21/2002 SNAJARRO 00000040 181945 10129773
02 FC:966 666.00 CR

PTO-1556
(5/87)

*U.S. Government Printing Office: 2001 — 481-697/59173

PATENT APPLICATION FEE DETERMINATION RECORD
Effective October 1, 2001

Application or Docket Number: A52D-P01-617

CLAIMS AS FILED - PART I

	(Column 1)	(Column 2)
TOTAL CLAIMS		
FOR	NUMBER FILED	NUMBER EXTRA
TOTAL CHARGEABLE CLAIMS	6 minus 20=	*
INDEPENDENT CLAIMS	5 minus 3 =	* 2
MULTIPLE DEPENDENT CLAIM PRESENT		☐

* If the difference in column 1 is less than zero, enter "0" in column 2

SMALL ENTITY TYPE ☐		OR	OTHER THAN SMALL ENTITY	
RATE	FEE		RATE	FEE
BASIC FEE		OR	BASIC FEE	890
X$ 9=		OR	X$18=	
X42=		OR	X84=	168
+140=		OR	+280=	280
TOTAL		OR	TOTAL	1338

CLAIMS AS AMENDED - PART II

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM ☐				

SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM ☐				

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT C

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM ☐				

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20."
***If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3."
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

MULTIPLE DEPENDENT CLAIM FEE CALCULATION SHEET

(FOR USE WITH FORM PTO-875)

SERIAL NO.	FILING DATE

APPLICANT(S)

CLAIMS

	AS FILED		AFTER 1st AMENDMENT		AFTER 2nd AMENDMENT	
	IND.	DEP.	IND.	DEP.	IND.	DEP.
1	1					
2		1				
3		2				
4		3				
5		4				
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7		6				
8		7				
9		8				
10		9				
11	1					
12	1					
13	1					
14	1					
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TOTAL IND.	5					
TOTAL DEP.	11					
TOTAL CLAIMS	16					

	*		*		*	
	IND.	DEP.	IND.	DEP.	IND.	DEP.
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98						
99						
100						
TOTAL IND.						
TOTAL DEP.						
TOTAL CLAIMS						

PTO-1360 (5-78)

*MAY BE USED FOR ADDITIONAL CLAIMS OR AMENDMENTS

U.S. DEPARTMENT of COMMERCE
Patent and Trademark Office

Docket No.: ASZD-P01-617
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Dearn et al.

Application No.: Not Yet Assigned

Group Art Unit: N/A

Filed: May 9, 2002

Examiner: Not Yet Assigned

For: PHARMACEUTICAL FORMULATIONS CONTAINING ZOLMITRIPTAN

INFORMATION DISCLOSURE STATEMENT (IDS)

Commissioner for Patents
Washington, DC 20231

Dear Sir:

Pursuant to 37 CFR 1.56, the attention of the Patent and Trademark Office is hereby directed to the references listed on the attached PTO/SB/08. It is respectfully requested that the information be expressly considered during the prosecution of this application, and that the references be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

This Information Disclosure Statement accompanies the new patent application submitted herewith.

A copy of each reference on PTO/SB/08 is attached.

A summary/abstract translation of the non-English language references is enclosed.

While the information and references disclosed in this Information Disclosure Statement may be "material" pursuant to 37 CFR 1.56, it is not intended to constitute an admission that any patent, publication or other information referred to therein is "prior art" for this invention unless specifically designated as such.

Application No.: Not Yet Assigned

Docket No.: ASZD-P01-617

In accordance with 37 CFR 1.97(g), the filing of this Information Disclosure Statement shall not be construed to mean that a search has been made or that no other material information as defined in 37 CFR 1.56(a) exists. It is submitted that the Information Disclosure Statement is in compliance with 37 CFR 1.98 and the Examiner is respectfully requested to consider the listed references.

The Commissioner is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 18-1945, under Order No. ASZD-P01-617. A duplicate copy of this paper is enclosed.

Dated: May 9, 2002

Respectfully submitted,

By _____

David P. Halstead, Ph.D.
Registration No.: 44,735
ROPES & GRAY
One International Place
Boston, Massachusetts 02110-2624
(617) 951-7000
(617) 951-7050 (Fax)
Agent for Applicant

File: ASZD-P01-617

New U.S. Patent Application
Filed: May 9, 2002
Title: Pharmaceutical Compositions Containing Zolmitriptan
Inventors: Dearn et al.
Our Reference No.: ASZD-P01-617
Express Mail No.: EL 934 406 177 US
Customer No.: 28120

Certificate of Express Mailing

I hereby certify that the documents addressed to Box PCT (DO/EO/US), Commissioner for Patents, Washington, D.C. 20231, enclosed in Express Mail package (Label No. EL 934 406 177 US) were deposited with the US Postal Service on the date identified below.

May 9, 2002
Date

Name: Phil Fantasia

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 04 September 2001 (04.09.01)	
International application No. PCT/GB00/04528	**Applicant's or agent's file reference**
International filing date (day/month/year) 28 November 2000 (28.11.00)	**Priority date** (day/month/year) 03 December 1999 (03.12.99)
Applicant DEARN, Alan, Roy et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

08 June 2001 (08.06.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

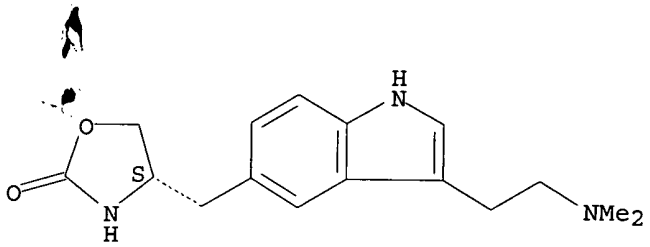
The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Olivia TEFY
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/331 (July 1992)

GB0004528

L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN 139264-17-8 REGISTRY
CN 2-Oxazolidinone, 4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-, (4S)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 2-Oxazolidinone, 4-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-, (S)-
OTHER NAMES:
CN (S)-4-[[3-[2-(Dimethylamino)ethyl]-1H-indol-5-yl]methyl]-2-oxazolidinone
CN 311C90
CN BW 311C90
CN **Zolmitriptan**
CN Zomig
FS STEREOSEARCH
MF C16 H21 N3 O2
CI COM
SR CA
LC STN Files: ADISINSIGHT, ADISNEWS, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CHEMCATS, CIN, DDFU, DIOGENES, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IPA, MEDLINE, MRCK*, PHAR, PHARMASEARCH, PROMT, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

185 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
188 REFERENCES IN FILE CAPLUS (1962 TO DATE)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/GB 00/ 04528	International filing date *(day/month/year)* 28/11/2000	(Earliest) Priority Date *(day/month/year)* 03/12/1999
Applicant ASTRAZENECA AB		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

[ ] the text is approved as submitted by the applicant.

[X] the text has been established by this Authority to read as follows:

PHARMACEUTICAL FORMULATIONS CONTAINING ZOLMITRIPTAN

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. –

[ ] as suggested by the applicant.

[ ] None of the figures.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

INTERNATIONAL SEARCH REPORT

International Application No
[redacted]T/GB 00/04528

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/4045 A61K9/00 A61P25/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 636 623 A (WELLCOME) 1 February 1995 (1995-02-01) cited in the application claims 1,5-10,13 page 5, line 2 - line 41 page 18, line 17 - line 44 page 29, line 45 -page 30, line 34 page 4, line 18 - line 30 ---	1,3,5,7, 8,11,13, 14
A	WO 98 02187 A (FARMARC) 22 January 1998 (1998-01-22) claims 1,2,7,9,10 tables examples 1,15 --- -/--	1,11-14

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 May 2001	16/05/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Scarponi, U

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
[redacted]T/GB 00/04528

C.(Continuation) DOCUMENTS CONSI[redacted]ED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	GB 2 315 673 A (MERCK) 11 February 1998 (1998-02-11) claims 1,4,6,9,11,12,15 page 3, line 15 - line 28 page 4, line 10 - line 18 page 5, line 6 - line 17 page 6, line 32 -page 7, line 25 examples 11-14 ---	1-14
A	WO 98 34595 A (JAGO PHARMA) 13 August 1998 (1998-08-13) claims 1,9,15,21,25,27 example 12 -----	1-14

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
T/GB 00/04528

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
T/GB 00/04528

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9834595 A		AU 5649698 A	26-08-1998
		EP 1014943 A	05-07-2000
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Form PCT/ISA/210 (patent family annex) (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
Z70617-1 WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB 00/ 04528	28/11/2000	03/12/1999
International Patent Classification (IPC) or national classification and IPC		
A61K31/4045		
Applicant		
ASTRAZENECA AB et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This **REPORT** consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by **ANNEXES**, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consists of a total of _____ sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☐ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
08/06/2001	25.03.02
Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	A. Oberhauser Andrea Oberhauser

I. Basis of the report

The basis of this international preliminary examination is the application as originally filed.

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The question of whether the claimed invention appears to be novel, to involve an inventive step, or to be industrially applicable has not been and will not be the subject of the international preliminary examination in respect of the claims corresponding to inventions or groups of inventions for which additional search fees may have not been paid, and consequently may have not been searched (Article 17(3)(a) and Rule 66.1(e) PCT; see also international search report).

IV. Lack of unity of invention

The objection as to lack of unity raised in the international search report is maintained. The reasons for the objection are the same as those indicated in the international search report.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability

To the extent that the international preliminary examination has been carried out (see item III above), the following is pointed out:

In light of the documents cited in the international search report, it is considered that the invention as defined in at least some of the claims, which have been the subject of an international search report, does not appear to meet the criteria mentioned in Article 33(1) PCT, i.e. does not appear to be novel and/or to involve an inventive step (see international search report, in particular the documents cited X and/or Y and corresponding claim references).

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/04528

I. Basis of th report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-7 as originally filed

Claims, No.:

1-14 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 7.

because:

☒ the said international application, or the said claims Nos. 7 with regard to IA relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-14
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-14
Industrial applicability (IA)	Yes:	Claims	1-6, 8-14

No: Claims

2. Citations and explanations
see separate sheet

1. Concerning section III

Claim 7 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

2. Concerning section V

This opinion is based on the following documents cited in the International Search Report:

D1: GB-A-2 315 673 (MERCK) 11 February 1998 (1998-02-11)
D2: EP-A-0 636 623 (WELLCOME) 1 February 1995 (1995-02-01) cited in the application

2.1 Industrial applicability, Art. 33(4) PCT

For the assessment of the present **claim 7** on the question of whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

2.2 Lack of inventive step, Art. 33(3) PCT

The subject-matter of **claim 1** cannot be considered inventive in light of the disclosures in the prior art discussed below.

D2 discloses compositions of 5-HT1-like agonists, suitable for intranasal administration, that can be used in *"....the prophylaxis or treatment of clinical conditions for which a 5-HT1-like receptor agonist is indicated, for example migraine"* (pg. 5, line 20-21 and 34-36). Physiologically acceptable salts of the compounds are mentioned on pg. 4, line 25-28, and include those derived from citric acid. An intranasal formulation in citrate buffer and pH adjusted to 7 with hydrochloridric acid is described on pg. 30.

Pharmaceutical compositions suitable for intranasal administration comprising zolmitriptan

and a pharmaceutically acceptable carrier are disclosed in **D1** (abstract and pgs. 3-4 and 7). Examples 11-14 (pg. 20) describe intranasal formulations containing lidocaine and rizatriptan. The latter, like zolmitriptan, belongs to the triptan family and is also used for the treatment of migraine (see D1 and description of the present application, pg. 1). The formulations described in said examples contain sulphuric acid and rizatriptan in a ratio of 1:5.5, strongly suggesting that the pH of this formulation is less than 7.

From the above it is clear that pharmaceutical formulations, suitable for intranasal administration, comprising zolmitriptan, are well known in the art. Furthermore, the pH of the formulations discussed in the prior art seems to be below 7. Therefore, the provision of a pharmaceutical formulation according to **claim 1**, does not appear to involve an inventive step. The same applies to **claims 3-11, 13 and 14**.

Claims 2 and 12 also lack inventive step because the optimization of the pH range is not regarded as inventive, unless a special effect, such as an improvement in the delivery or stability of zolmitriptan, compared to the formulations in the prior art, is shown in the claimed range.

2.3 Clarity, Art. 6 PCT

It should be noted that the expression *"suitable for"* is not regarded as restricting the claim to the use given (see PCT Guidelines C-III, 4.8). In order to restrict this claim to the specific use mentioned therein (intranasal administration), *"suitable for"* should be replaced by *"for"*.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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Published:
— *With international search report.*
— *Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/39772 A1

(54) Title: PHARMACEUTICAL FORMULATIONS CONTAINING ZOLMITRIPTAN

(57) Abstract: A pharmaceutical formulation of the 5HT1-agonist, zolmitriptan, for use in intranasal administration. The formulation is useful in treating migraine and related disorders.

PHARMACEUTICAL FORMULATIONS CONTAINING ZOLMITRIPTAN

The present invention relates to new pharmaceutical formulations, their preparation and their use in treatment of disease. In particular the present invention relates to pharmaceutical formulations of the anti-migraine drug zolmitriptan for nasal application.

Zolmitriptan has the chemical name (S)-4-{{3-[2-(dimethylaminoethyl]-1H-indol-5-yl]methyl]-2-oxazolidinone. Zolmitriptan is a selective 5HT1-receptor agonist. The 5HT1-receptor mediates vasoconstriction and thus modifies blood flow to the carotid vascular bed. 5HT1-receptor agonists are beneficial in the treatment (including prophylaxis) of disease conditions wherein vasoconstriction in the carotid vascular bed is indicated, for example migraine, cluster headache and headache associated with vascular disorders, hereinafter referred to collectively as 'migraine'. Zolmitriptan has been developed for the acute treatment of migraine in the form of a 2.5 mg and 5 mg tablet intended to be taken up to a maximum of 15 mg per day.

Although zolmitriptan is a successful drug of considerable benefit to migraine sufferers, there is a continuing need for alternative methods for the direct treatment of migraine and the prophylactic treatment of migraine. In particular, patients suffering from migraine or the onset of migraine need fast relief of their suffering.

Zolmitriptan is a member of a class of drugs known as triptans, for example sumatriptan, naratriptan and rizatriptan, which are prescribed for the treatment of migraine. The leader in terms of sales is sumitriptan which has been marketed as an oral formulation. A subcutaneous formulation was also developed; this was more efficacious (P Tfelt-Hansen, Cephalalgia 1998, Vol 18(8), page 532-8) and gave a faster onset of action but was not so acceptable to the patient. An intranasal spray was also developed. This was more user-friendly than the subcutaneous injection but was reported to be less effective in reducing the symptoms of migraine attacks (C Dahlof, Cephalalgia 1998; 18(5): 278-282). Also, many patients reported an unpleasant bitter taste after using the nasal spray.

The present inventors sought a formulation of zolmitriptan that achieved fast relief whilst maintaining high efficacy. They also sought a formulation that, for the wide variety of patients that suffer from migraines, had a more acceptable route of administration than a subcutaneous injection. Clearly, the thought of a subcutaneous injection may dissuade many patients from taking appropriate and necessary treatment. Furthermore, the inventors sought

a formulation that was convenient, effective and acceptable to the patient and did not cause any unnecessary irritancy or side-effects.

USP5466699 discloses a class of chemical compounds for the treatment and prophylaxis of migraine. USP5466699 discloses that this class of compounds may be formulated for oral, sublingual, buccal, parenteral (for example subcutaneous, intramuscular or intraveneous), rectal, topical and intranasal administration and examples of such possible formulations, including an example of an intranasal formulation, are disclosed. The intranasal formulation consists of an active ingredient, methyl hydroxybenzoate (0.2%), propyl hydroxybenzoate (0.02%), citrate buffer and sufficient hydrochloric acid to take the pH to 7.

The present inventors devised an intranasal formulation of zolmitriptan that provided effective and improved fast relief for migraine sufferers. Although, the inventors do not wish to be bound by theory, it is thought that this is at least partly due to the direct mucosal absorption of a significant proportion of zolmitriptan administered by the intranasal route.

Furthermore, studies with an intranasal formulation of zolmitriptan having a pH of above 7.0, at a pH of 7.4, showed the stability of that formulation would not be acceptable over extended periods of time.

The present inventors provided an improved rapid onset of action with a stable intranasal formulation of zolmitriptan having a pH of below 7.0. In addition, this formulation was acceptable to the general patient population and did not cause unnecessary irritancy or side effects.

Accordingly the present inventors provide a pharmaceutical formulation suitable for intranasal administration which comprises zolmitriptan and a pharmaceutically acceptable carrier wherein the pH of the formulation is less than 7.0.

The zolmitriptan formulation for intranasal administration is generally prepared as an aqueous formulation and typically is buffered. Suitable buffering agents include citric acid, phosphates such as disodium phosphate (for example the dodecahydrate, heptahydrate, dihydrate and anhydrous forms) or sodium phosphate and mixtures thereof (for example McIlvaine's buffer which is a mixture of citric acid and disodium phosphate).

In a particular aspect the pH of the pharmaceutical formulation of zolmitriptan is below 6.0, for example in the range 3.5 to 5.5, and in particular in the range 4.5 to 5.5. In a particular aspect the pH of the formulation is about 5.0.

In addition to the buffer, the zolmitriptan formulation may contain other ingredients typically found in intranasal formulations, such as antioxidants for example sodium metabisulphite, taste-masking agents such as menthol and sweetening agents for example dextrose, glycerol, saccharin and sorbitol.

In another aspect the present invention provides an aqueous solution of zolmitriptan in a buffer at a pH of less than 7.0 in particular at a pH below 6.0, for example in the range 3.5 to 5.5 and in particular in the range 4.5 to 5.5, for example at about 5.0. In particular the present invention provides an aqueous solution of zolmitriptan in a buffer of citric acid and phosphate at a pH of less than 7.0, in particular at a pH below 6.0, for example in the range 3.5 to 5.5 and in particular in the range 4.5 to 5.5, for example at about 5.0.

The pharmaceutical formulation of the present invention may be co-administered (simultaneously or sequentially) with one or more pharmaceutical agents of value in treating migraine or related disease conditions.

The pharmaceutical formulations of the invention will normally be administered to humans so that, for example a unit dose of about 0.5 mg to 15 mg (for example 0.5 mg, 1.0 mg, 2.5 mg, 5.0 mg and 10mg) of zolmitriptan is delivered to the patient in need thereof. The concentration and volume of the formulation may vary as known in the intranasal art, typically a volume of 50 to 250µl is administered, for example 50µl or 100µl (in one spray or in two 50µl sprays - one for each nostril), The precise dose delivered depends on various factors known in the art including the weight, age and sex of the patient being treated and on the particular migraine disease condition being treated. Such a unit dose may be taken at any stage in the onset of, or during the course of, a migraine attack. Such a unit dose may be taken as needed, typically from 1 to 3 times a day.

The pharmaceutical formulations of this invention may be prepared by dissolving zolmitriptan in an acidic medium, for example aqueous citric acid, thereby forming the citrate salt of zolmitriptan, and taking the pH to the desired value by adding a suitable agent for example a phosphate. The resultant buffered solution is typically manufactured to ensure that it contains a low bioburden or to ensure that it is sterile. Typically the solution is sterilised for example by passing through a sterile filter (for example 0.2 µm) or by autoclaving. Preferably, the solution is purged with nitrogen, and overlaid with nitrogen in the primary pack, to minimise the possibility of degradation. Alternatively, another inert gas, such as argon, could be used. Therefore in another aspect the present invention provides a sterile

pharmaceutical formulation suitable for intranasal administration which comprises zolmitriptan and a pharmaceutically acceptable carrier wherein the pH of the formulation is less than 7.0.

The pharmaceutical formulations of the invention are typically filled into a suitable administration device capable of delivering a unit dose amount of zolmitriptan to the patient in need thereof. Such administration devices include those available commercially and the device disclosed in UK Registered Design 2071555. Therefore in a another aspect, the present invention provides an intranasal administration device containing zolmitriptan and a pharmaceutically acceptable carrier wherein the pH of the formulation is less than 7.0.

The filled intranasal administration device may be packaged to provide protection from light. Accordingly in yet a further aspect, the present invention provides an intranasal administration device containing zolmitriptan and a pharmaceutically acceptable carrier in light-protecting packaging, for example in foil pouches. In an alternative aspect, the device itself is a dark colour to provide protection from light, for example, a dark blue colour.

Therefore in a further aspect the present invention provides a pharmaceutical formulation suitable for intranasal administration which comprises zolmitriptan and a pharmaceutically acceptable carrier wherein the pH of the formulation is less than 7.0 for use in a method of therapeutic treatment of the human or animal body.

In yet a further aspect the present invention provides a method of treating a disease condition wherein agonism of 5HT1-receptors is beneficial which comprises administering an effective amount of a pharmaceutical formulation suitable for intranasal administration which comprises zolmitriptan and a pharmaceutically acceptable carrier wherein the pH of the formulation is less than 7.0. The present invention also provides the use of zolmitriptan and a pharmaceutically acceptable carrier in the manufacture of a pharmaceutical formulation suitable for intranasal administration wherein the pH of the formulation is less than 7.0.

Zolmitriptan used in the formulations of the present invention may be prepared according to the disclosures of WO 91/18897 and WO 97/06162.

Examples 1-4

Zolmitriptan is dissolved in an aqueous solution of citric acid, 0.4M disodium phosphate dodecahydrate is added to pH 5.0 and water of injection is added to the desired volume. In this manner solutions with concentrations of zolmitriptan of 5 mg/mL, 10

mg/mL, 25 mg/mL and 50 mg/mL are prepared. The solution is filtered through a sterilizing grade filter (0.2 μm), and filled into USP/Ph Eur Type 1 glass vials (nominal spray volume 100μL) which are closed with chlorobutyl stoppers.

Table 1

Nasal Spray Nominal Strength	0.5 mg	1 mg	2.5 mg	5 mg
Solution Concentration	5 mg/ml	10 mg/ml	25 mg/ml	50 mg/ml
Zolmitriptan	0.5	1.0	2.5	5.0
Citric acid, anhydrous USP/Ph Eur	1.11	1.29	1.79	2.60
Disodium phosphate dodecahydrate USP/Ph Eur*	qs to pH 5.0	qs to pH 5.0	qs to pH 5.0	qs to pH 5.0
Water for Injections USP/Ph Eur	to 0.1 ml	to 0.1 ml	to 0.1 ml	to 0.1 ml

* Added as a 0.4 M solution of Disodium Phosphate Dodecahydrate Ph Eur/USP diluted with purified water USP/Ph Eur.

The vials are assembled into the unit dose nasal spray device disclosed in UK Registered Design 2071555. This device comprises a vial holder, an actuation device and a protection cap. The assembled device may be used to deliver unit doses of zolmitriptan of 0.5 mg, 1.0 mg, 2.5 mg or 5.0 mg in a single administration. The filled nasal spray device is packaged into a plastic tray and placed inside a carton to provide protection from the light.

Examples 5-8

Zolmitriptan is dissolved in an aqueous solution of citric acid, 0.4M disodium phosphate is added to pH 5.0 and water of injection is added to the desired volume. In this manner solutions with concentrations of zolmitriptan of 5 mg/mL, 10 mg/mL, 25 mg/mL and 50 mg/mL are prepared. The solution is filtered and filled into USP/Ph Eur Type 1 glass vials (nominal spray volume 100μL) which are closed with chlorobutyl stoppers.

Table 1

Nasal Spray Nominal Strength	0.5 mg	1 mg	2.5 mg	5 mg
Solution Concentration	5 mg/ml	10 mg/ml	25 mg/ml	50 mg/ml
Zolmitriptan	0.5	1.0	2.5	5.0
Citric acid, anhydrous USP/Ph Eur	1.11	1.29	1.79	2.60
Disodium phosphate USP/Ph Eur*	qs to pH 5.0	qs to pH 5.0	qs to pH 5.0	qs to pH 5.0
Purified Water USP/Ph Eur	to 0.1 ml	to 0.1 ml	to 0.1 ml	to 0.1 ml

* Added as a 0.4 M solution of Disodium Phosphate Ph Eur/USP diluted with purified water for injection.

The vials are autoclaved at 121°C for 15 minutes. They are then assembled into the unit dose nasal spray device disclosed in UK Registered Design 2071555. This device comprises a vial holder, an actuation device and a protection cap. The assembled device may be used to deliver unit doses of zolmitriptan of 0.5 mg, 1.0 mg, 2.5 mg or 5.0 mg in a single administration. The filled nasal spray device is packaged into a plastic tray and placed inside a carton to provide protection from the light.

Example 9

The patient removes the packaging from the nasal spray device, and then removes the protection cap. The patient then inserts the nozzle of the device into a nostril and actuates it to administer a single dose.