PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 10/518,016	Filing Date 07/06/2005	☐ To be Mailed

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☐		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☒ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	**300**
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	**300**

APPLICATION AS AMENDED – PART II

		(Column 1)		(Column 2)	(Column 3)	SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
	08/16/2011	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
AMENDMENT	Total (37 CFR 1.16(i))	* 47	Minus	** 51	= 0	X $ =		OR	X $52=	0
	Independent (37 CFR 1.16(h))	* 5	Minus	***6	= 0	X $ =		OR	X $220=	0
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	**0**

		(Column 1)		(Column 2)	(Column 3)					
		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
AMENDMENT	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/GLORIA TRAMMELL/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/518,016	07/06/2005	Amar Lulla	PAC/20632 US (4137-04700)	4912

30652 7590 08/04/2011

CONLEY ROSE, P.C.
5601 GRANITE PARKWAY, SUITE 750
PLANO, TX 75024

EXAMINER	
NIELSEN, THOR B	

ART UNIT	PAPER NUMBER
1616	

MAIL DATE	DELIVERY MODE
08/04/2011	PAPER

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

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

Interview Summary	Application No.	Applicant(s)
	10/518,016	LULLA ET AL.
	Examiner	Art Unit
	THOR NIELSEN	1616

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

(1) *THOR NIELSEN*.	(3) *Mr. Rodney Carroll*.
(2) *Johann Richter*.	(4) *Ms. Jerry Walker* .

Date of Interview: *01 August 2011*.

Type: a)☒ Telephonic b)☐ Video Conference
c)☐ Personal [copy given to: 1)☐ applicant 2)☐ applicant's representative]

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

Claim(s) discussed: *1,2,4-22,26,27,30,35-38,44,45 and 53-56*.

Identification of prior art discussed: *Cramer (EP0780127)*.

Agreement with respect to the claims f)☐ was reached. g)☒ was not reached. h)☐ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *See Continuation Sheet*.

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN A NON-EXTENDABLE PERIOD OF THE LONGER OF ONE MONTH OR THIRTY DAYS FROM THIS INTERVIEW DATE, OR THE MAILING DATE OF THIS INTERVIEW SUMMARY FORM, WHICHEVER IS LATER, TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

8/1/11	/Johann R. Richter/ Supervisory Patent Examiner, Art Unit 1616	

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

Continuation of Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: Mr. Carroll explained that a product encompassed by the claims has been commercialized in India under the name "Duonase" and that the product has been licensed to Meda Pharmaceuticals and is in Phase III trials. He further provided a preview of intended amendments, supplemental data, and topics of forthcoming Declarations. The amendments would remove the term "fluticasone" from claim 1 and leave fluticasone esters and would further require that the formulation be suitable for nasal use. He said that the company scientists have found that Example III of the Cramer reference is inoperable because the formulation is inhomogeneous, is delivered as a jet rather than a diffuse spray, and is hypertonic and that this analysis would be provided. The Declarations would address surprizing results, commercial success, and a long-felt need in the art. Also, some amendments directed to clarifying the specification will be forthcoming. He expects to file the repsonse at or before the deadline.

.

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/518,016	07/06/2005	Amar Lulla	PAC/20632 US (4137-04700)	4912

30652 7590 02/16/2011

CONLEY ROSE, P.C.
5601 GRANITE PARKWAY, SUITE 750
PLANO, TX 75024

EXAMINER	
NIELSEN, THOR B	

ART UNIT	PAPER NUMBER
1616	

MAIL DATE	DELIVERY MODE
02/16/2011	PAPER

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

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

Office Action Summary	Application No.	Applicant(s)	
	10/518,016	LULLA ET AL.	
	Examiner	Art Unit	
	THOR B. NIELSEN	1616	

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

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 September 2010*.

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

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

Disposition of Claims

4)☒ Claim(s) *1,2,4,6-22,26,27,30,35-38,44,45 and 53-56* is/are pending in the application.

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

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,6-22,26,27,30,35-38,44,45 and 53-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

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

Application Papers

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

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

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

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/24/2010; 10/19/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Examination

In brief, the claims were initially reviewed and a non-Final rejection mailed on January 23, 2009. In that action, the claim set was restricted and claims 23, 24, and 46-52 were withdrawn from consideration. Then-pending claims 1-4, 7, 9-10, 12-21, 30-32, and 44-45 were rejected as anticipated by EP 0780127 (Cramer). In that same action, then-pending claims 5 and 35-38 were rejected as obvious over Cramer; claims 22 and 26-27 were rejected as obvious over Cramer in view of US 6,294,153 (Modi); claims 1-3 and 6 were rejected as obvious over US 6,391,340 (Malmqvist-Granlund); and claims 28-29 were rejected as obvious over Cramer in view of US 6,017,963 (Alfonso). No claims were allowed.

In response, Applicant amended the claims, submitted a Declaration under 37 CFR 1.132, and argued for patentability. Of note, the Applicant incorporated the limitations of claim 5, which had not been rejected as anticipated, into claim 1.

A Final Office Action was mailed on April 28, 2010, rejecting then-pending claims 1-2, 4, 7-21, 30, 35-38, 44-45, and 53-56 as obvious over Cramer. In addition, claims 22 and 26-27 were rejected as obvious over Cramer in view of Modi; claims 1-2 and 6 were rejected as obvious over Cramer in view of US 6416743 (Fassberg); and claims 1, 25, 28-29 were rejected as obvious over Cramer in view of Alfonso. No claims were allowed.

The current Action is responsive to the Amendment and Response to Final Rejection filed on September 24, 2010, and the revised Declaration under 37 CFR 1.132 by Geena Malhotra, with Exhibits A-D, dated September 23, 2010.

A Request for Continuing Examination was filed on September 27, 2010.

The examiner in this application has changed. Please address future correspondence accordingly.

Status of Claims

Claims 1-2, 4, 6-22, 26-27, 30, 35-38, 44-45, and 53-56 are pending. Of these claims, claims 26, 27, and 30 were amended in the most recent response. The Amendments are entered of right.

Anticipation rejection, reinstated in part and new in part

In the Office Action that was mailed on January 23, 2009, claim 5, directed to a steroid range, was not rejected as *anticipated* by Cramer. That was an error, because, as discussed further below, Cramer discloses the claimed amounts of steroid. This examiner recognizes that the correction of the error places an additional burden on the Applicant.

The rejection of claims 1-2, 9-10, 12-21, 30, 45, and 55-56 as obvious over Cramer is **withdrawn** in favor of the following anticipation rejection.

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 1-2, 9-10, 12-21, 30, 45, and 55-56 are rejected as anticipated by Cramer.

Cramer is directed generally to **a nasal spray containing a steroid and an antihistamine**. Abstract. The compositions are suitable **for treatment of symptoms associated with seasonal or perennial allergic rhinoconjunctivitits**. At page 2, lines 28-30. Cramer discloses a pharmaceutical composition that can have **a safe and effective amount of Azelastine**. *At* page 2, lines 36-44, esp. line 42. The composition can also have **a safe and effective amount of Fluticasone**. Id., esp. line 39. The Fluticasone can be present in **an amount from about 0.001 to about 0.2 wt. % or from about 0.01 to about 0.1 wt. %**. *At* page 3, lines 19-20 and page 2, line 58. The disclosed compositions are prepared in **saline or isotonic glucose** (see Examples). Such dilute solutions are essentially the same in weight/volume units, because the density of the solution differs little from the density of water. Also, the disclosure uses the broadening term "about." Cramer discloses **Azelastine hydrochloride**. *At* page 6, Example II, esp. line 33. The amount of Azelastine can be **from about 0.01 to about 4 wt. %, preferably from about 0.01 % to about 1 wt. %**. *At* page 3, lines 28-30. Cramer discloses that the composition can have **a surfactant**, e.g. **a polysorbate**, in a usual amount from 0.5 to 10 wt. %. *At* page 5, lines 11-15. The compositions can have

sodium chloride, **dextrose/glucose**, **polypropylene glycol**, among other named agents, for controlling **isotonicity**. *At* page 4, lines 50-55. Cramer discloses compositions with a **thickener** which can be **a cellulose derivative** (page 4, line 56 to page 5, line 2), **a buffer** (page 3, lines 47-49), and **a preservative** (Id.). The buffer can have **citric acid**, and hence **citrate**. *At* page 4, lines 50-53. The pH can be from about 4.5 to about 9, preferably **from about 6 to about 7**. *At* page 2, line 57. Cramer envisions **solutions** (e.g. page 5, line 57) and **suspensions** (e.g. page 5, lines 27-30). Cramer discloses the **preparation** of nasal sprays. See Examples.

This rejection is proper under *In re Petering,* 133 USPQ 275, 280 (CCPA 1962), in which disclosure of a genus of 20 related compounds rendered obvious a claim to one of those compounds. See also *In re Schaumann*, 197 USPQ 5, 7 (CCPA 1978), which found a claim to one compound obvious over the disclosure of a genus having 105 compounds that encompassed the claim.

In the instant application, Cramer discloses a genus consisting of the combinations of six steroids and three antihistamines, thus corresponding to eighteen combinations. That the antihistamines are available in various salt forms and that the steroids are available in various esters does not negate the validity of the rejection, because the salts and esters are well-known variants. Moreover, Cramer specifically discloses the chloride salt of Azelastine. *In re Ruschig,* 145 USPQ 274 (1965) is not *in point* because Cramer defines a small recognizable class with common properties, unlike the fact situation in *Ruschig.*

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The rejection of claim 44 over Cramer, as stated in the Office Action of April 28, 2010, is **withdrawn** because the claim depends from a claim not rejected over Cramer.

The rejection of claims 1, 25, and 28-29 as obvious over Cramer in view of US 6,017,963 (Alfonso) (of record) is **withdrawn** because of the cancellation of claims 25, and 28-29.

The rejection of claims 4, 7, 8, 11, 35, 36, 37, 38, 53, and 54 as obvious over Cramer, as stated in the Office Action of April 28, 2010, is **maintained** for reasons of record.

The rejection of claims 22 and 26-27 as obvious over Cramer in view of US6294153 (Modi) (of record) is **maintained** for reasons of record.

The rejection of claims 1, 2, and 6 as obvious over Cramer in view of US 6,416,743 (Fassberg) (of record) is **maintained** for reasons of record.

Claim 44 is newly rejected over Cramer in view of US6294153 (Modi) (of record).

Determination of the scope and content of the prior art (MPEP 2141.01)

The disclosure of Cramer is discussed above. Modi teaches aerosol formulations for nasal delivery comprising pharmaceutical agents (i.e. anti-inflammatories, steroids, etc.), water, excipients and a propellant. Abstract and column 3, lines 30-40. Improved penetration into the nasal cavity and absorption of the

formulations can be achieved by mixing the formulation with propellants such as tetrafluroethane, etc., especially when delivered through aerosol devices (i.e. MDI). Column 2, lines 5-24.

Ascertainment of the difference between the prior art and the claims (MPEP 2141.02)

Cramer does not teach aerosol sprays or metered dose inhalers (MDI). As discussed above, Modi teaches aerosols and MDI and thus, Modi cures the deficiency in Cramer.

Finding of *prima facie* Obviousness Rationale and Motivation

(MPEP 2142-2143)

One of ordinary skill in the art, familiar with the disclosure of Cramer, would have been motivated to make a composition further comprising a propellant because Modi suggests that adding propellants to nasal formulations can increase penetration and absorption in the nasal cavity. Thus, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to make a composition further comprising a propellant for the purpose of increasing penetration of active formulations into the nasal cavity. Therefore, the invention as claimed in claim 44 would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made because the prior art is fairly suggestive of the claimed invention.

Response to Remarks and Arguments

Applicant's arguments with regard to obviousness of claims 1-2, 9-10, 12-21, 30, 45, and 55-56 is mooted by the new or reinstated anticipation rejection. Thus,

Applicant's arguments will be considered in view of the remaining claims: 4, 6-8, 11, 22, 26-27, 35-38, 44, 53, and 54.

A. Argument for lack of establishment of a prima facie *case of obviousness*

Applicant argues that the instant claims as amended are **A.** patentable over the art of record and **B.** patentable in view of objective evidence of nonobviousness. In particular, Applicant asserts that the examiner has not established a *prima facie* case of obviousness and that objective evidence shows that a pharmaceutical formulation comprising Azelastine (an antihistamine) and Fluticasone (a corticosteroid) displays unexpectedly beneficial properties, is commercially successful, and fills a long felt but unsolved need. *At* page 10. Each of these assertions is discussed in detail below.

In the Office Action dated January 23, 2009, the Examiner observed that the prior art reference (Cramer) disclosed a nasal spray comprising the combination of a glucocorticoid and an antihistamine. Moreover, Cramer disclosed six corticosteroids and three antihistamines, but did not exemplify the combination of Azelastine and Fluticasone. The examiner then stated that it was well within the means for one of ordinary skill in the art to try the instant combination as there are a small number of actives to choose from. *At* pages 14-15.

Applicant characterizes the rejection as an obvious-to-try rejection. Amendment of September 24, 2010, *at* page 11. Applicant, quoting *In re Kubin,* further asserts that an obvious-to-try rejection requires an indication of which parameters were critical or which of many possible choices is likely to be successful. 90 USPQ2d 1417, 1423 (Fed. Cir. 2009) ('[W]here a defendant merely throws metaphorical darts at a board filled

with combinatorial prior art possibilities, court should not succumb to hindsight claims of obviousness.")

The Applicant's arguments are mooted by the reinstatement of a rejection for anticipation, above.

B. Argument for secondary considerations

Applicant argues in the alternative that secondary considerations render the instant claims, as amended, nonobvious over the art of record, and has provided a second Declaration (dated September 23, 2010) under 37 CFR 1.132, which has "amended values [that] represent clarifications and the remedying of typographical errors in the previously submitted data." *At* page 13.

Both the current and previous Declarations had the statement in which the Declarant "declare[d] 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 are made with the knowledge that willful false statements and the like so made are punishable by fine, imprisonment, or both . . . and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon." E.g., Declaration dated September 23, 2010, page 3.

Second Declaration under 37 CFR 1.132

In brief, the examiner observes the following items in the second Declaration:

1. Table I (of Exhibit A) shows the compositions of the Azelastine, Budesonide, the combination of Azelastine and Budesonide, Fluticasone, and the combination of

Azelastine and Fluticasone formulations. The values of some of the units and of the actual constituents have been changed from the Exhibit of the previous Declaration.

2. Table II (of Exhibit A) shows the initial assay of the five formulations described in Table I. Table II also shows the level of impurities in the initial formulations and after storage for either 1 month or 3 months under either of two conditions: 25 ℃ at 60 % relative humidity or 40 ℃ at 75 % relative humidity. (Note that Budesonide was stored for 2 months, rather than three months, and that no data was presented for Fluticasone or the combination of Azelastine and Fluticasone at one month at 25 ℃.) All the formulations, except for the combination of Azelastine and Budesonide were substantially stable. The Declaration states that the stability of the combination of Azelastine and Fluticasone was surprising. *At* page 2.

3. Six medical practitioners provided statements supporting and extolling the advantages and superior results associated with use of the combination formulation. In addition, some statements stated that the combination formulation provided a benefit that was not realized by previously existing products.

4. Information from a commercially available product (Duonase Nasal Spray from Cipla) was provided as Exhibit C, which reported the availability of a formulation comprising Fluticasone, Azelastine, benzalkonium chloride, and phenyl ethanol.

5. The Declaration provided a description of the testing method and the nature of the impurities detected.

6. The Declaration further provided a statement that, based on the data provided, the Declarant observed a beneficial stability when compared to the Azelastine and Budesonide compositions.

7. The Declaration also stated that the Declarant was not aware of another commercially available pharmaceutical formulation comprising an antihistamine and a steroid.

8. According to the Declaration, the instant application is licensed to Meda Pharmaceuticals.

Applicant argues that the [second] Declaration demonstrates that the claimed pharmaceutical formulation comprising Azelastine and Fluticasone has unexpected and beneficial stability. Applicant also argues that one of skill in the art would understand that improved product stability is extremely important in pharmaceutical compositions. Amendment, *at* page 14.

None of the above arguments are directed to the elements in the claims currently rejected for obviousness. Thus the examiner finds that all of the Applicant's arguments are addressed to the rejection as obvious over Cramer and are mooted by the rejection as anticipated over Cramer.

1. Argument that the combination of Azelastine and Fluticasone displays unexpected, beneficial results

Applicant further asserts that the Declaration's Exhibits B1 and B3 demonstrate that a formulation of Azelastine and Fluticasone has unexpected efficacy when

administered to patients, specifically that the product is very effective when compared [to] available other nasal sprays. *At* page 14, quoting an Exhibit. Applicant also notes that another physician wrote that the combination formulation "is very, very effective in all types of allergic rhinitis" and a "single drug was not effective as compared with the combination of both."

Again, the argument is mooted by the rejection of the claims as anticipated by Cramer.

Applicant also argues that the doctor's statements demonstrate a *synergistic* benefit in efficacy over Azelastine alone or Fluticasone alone.

The applicant is arguing a feature not claimed.

Response to alleged deficiencies of 1.132 Declaration

The Applicant recounts four deficiencies that were noted in the previous Office Action regarding the first Declaration under Rule 132.

Applicant states that the Office Action noted that there was no description of the testing method, assay utilized, or calculation of the impurity level. In response Applicant provided Exhibit D of the instant Declaration, which describes the method of identifying the impurities.

Two, Applicant provided, also in Exhibit D, the reference substances used for comparison with the impurities found in each composition. In particular, one Azelastine HCl impurity was monitored and nine Fluticasone propionate impurities were monitored.

Third, in response to the examiner's comment that the Applicant did not test against the closest prior art examples disclosed in Cramer, Applicant noted that Cramer

treated Fluticasone and Budesonide as alternatives. Thus, one of skill in the art would consider the appropriate comparative to be the one tested.

Fourth, Applicant addresses the examiner's comment that the compositions that contained Fluticasone also had the preservative phenyl ethanol, whereas the Budesonide compositions did not. The Applicant observes first that the impurity levels of the Azelastine, Budesonide, and Fluticasone solo formulations are similar, although the preservative is present in Fluticasone. Thus, Applicant asserts, the presence of phenyl ethyl alcohol did not serve to distinguish the stability of the Fluticasone sample from that of the Azelastine or Budesonide samples.

The arguments are not addressed to the limitations found in the claims that are currently rejected as obvious and are thus mooted by the anticipation rejection.

The Applicant further argues that the presence of phenyl ethyl alcohol in the Azelastine and Fluticasone composition cannot account for the observed dramatic increase in stability of this composition when compared to the Azelastine and Budesonide composition.

This argument is mooted by the current rejection.

The Applicant next provides excerpts from the *Handbook of Microbiological Quality Control* and an article entitled "Preservatives in Ophthalmic Formulations." The references do not mention the effect of preservatives on the chemical stability of the drug actives.

This argument is also mooted by the current rejection.

Applicant asserts that the Examiner's assertion that the preservative may have an effect on the chemical stability of the actives is a mere assumption, because the standard is whether the result or characteristic is necessarily present.

The argument is moot.

2. The combination of Azelastine and Fluticasone is commercially successful

Applicant asserts that a combination formulation of Azelastine and Fluticasone is commercially available. *At* page 19. Applicant also asserts that the doctor's statements and successful licensing support commercial success. *Id.*

Not unexpectedly, Applicant has not addressed how the elements found in the claims currently rejected as obvious are factors in the commercial success of the product. Rather, the argument appears directed to the elements of claim 1, and thus is moot.

3. The combination of Azelastine and Fluticasone fills a long-felt need

The Applicant asserts that despite Cramer's patent, no commercial formulation of an antihistamine and a steroid is available, even ten years later. *At* page 19.

The argument is not directed to the limitations found in claims currently rejected as obvious. Thus, the argument is moot.

Conclusion

All pending claims are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to THOR B. NIELSEN whose telephone number is

(571)270-3476. The examiner can normally be reached on Monday through Friday from 9:00 A.M. to 4:00 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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

Thor Nielsen
Patent Examiner

/Johann R. Richter/

Supervisory Patent Examiner, Art Unit 1616

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	10518016
Filing Date	2005-07-06
First Named Inventor	Amar Lulla
Art Unit	1616
Examiner Name	Kristie Latrice Brooks
Attorney Docket Number	PAC/20632 US (4137-04700)

U.S.PATENTS Remove

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

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

U.S.PATENT APPLICATION PUBLICATIONS Remove

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

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

FOREIGN PATENT DOCUMENTS Remove

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

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

NON-PATENT LITERATURE DOCUMENTS Remove

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

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /T.N./

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	10518016
	Filing Date	2005-07-06
	First Named Inventor	Amar Lulla
	Art Unit	1616
	Examiner Name	Kristie Latrice Brooks
	Attorney Docket Number	PAC/20632 US (4137-04700)

	1	ABPI Compendium of Data Sheets and Summaries of Product Characteristics, 1999-2000, Cover page, pg. 43 and Index Page 1882, Datapharm Publications Limited, London, Great Britain.	☐
	2	DYKEWICZ, MARK S., et al., "Diagnosis and Management of Rhinitis: Complete Guidelines of the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology," Annals of Allergy, Asthma, & Immunology, Vol. 81, November (Part II) 1998, pgs. 478 - 518.	☐
	3	Foreign communication from a related counterpart application - Notice of Opposition, EP Application 03738280.1, February 22, 2010, 22 pages.	☐

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

EXAMINER SIGNATURE

Examiner Signature	/Thor Nielsen/	Date Considered	02/09/2011

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

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

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /T.N./

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	10518016
Filing Date	2005-07-06
First Named Inventor	Amar Lulla
Art Unit	1616
Examiner Name	Kristie Latrice Brooks
Attorney Docket Number	PAC/20632 US(4137-04700)

U.S.PATENTS Remove

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

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

U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20020076382	A1	2002-06-20	Kaplan, et al.	
	2	20040136918	A1	2004-07-15	Garrett, et al.	
	3	20090291143	A1	2009-11-26	Lulla, et al.	
	4	20090318397	A1	2009-12-24	Lulla, et al.	

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

FOREIGN PATENT DOCUMENTS Remove

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

/Thor Nielsen/ 02/09/2011

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /T.N./

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	10518016
	Filing Date	2005-07-06
	First Named Inventor	Amar Lulla
	Art Unit	1616
	Examiner Name	Kristie Latrice Brooks
	Attorney Docket Number	PAC/20632 US(4137-04700)

	1							☐

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

NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	Office Action dated September 30, 2010, Application Serial No. 12/508,388 filed on July 23, 2009, 22 pages.	☐
	2	Office Action dated September 30, 2010, Application Serial No. 12/508,393 filed on July 23, 2009, 31 pages.	☐
	3	SCHMIDT, M. W. "The new topical steroid ciclesonide is effective in the treatment of allergic rhinitis." Journal of Clinical Pharmacology, 1999, vol. 39, pgs. 1062-1069.	☐
	4	Patent application entitled "Combination of azelastine and steroids," by Amar Lulla, et al., filed September 10, 2010 as serial number 12/879,515.	☐

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

EXAMINER SIGNATURE

Examiner Signature	/Thor Nielsen/	Date Considered	02/09/2011

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

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

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /T.N./

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	10518016
Filing Date	2005-07-06
First Named Inventor	Amar Lulla
Art Unit	1616
Examiner Name	Kristie Latrice Brooks
Attorney Docket Number	PAC/20632 US (4137-04700)

U.S.PATENTS Remove

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

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

U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20060110331	A1	2006-05-25	Dang, et al.	
	2	20070020330	A1	2007-01-25	Dang, et al.	
	3	20100152147	A1	2010-06-17	Fuge, et al.	

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

FOREIGN PATENT DOCUMENTS Remove

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

/Thor Nielsen/ 02/09/2011

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /T.N./

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	10518016
Filing Date	2005-07-06
First Named Inventor	Amar Lulla
Art Unit	1616
Examiner Name	Kristie Latrice Brooks
Attorney Docket Number	PAC/20632 US (4137-04700)

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

NON-PATENT LITERATURE DOCUMENTS [Remove]

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	HODGES, NORMAN, et al., "Antimicrobial Preservative Efficacy Testing," Handbook of Microbiological Quality Control, Pharmaceuticals and Medical Devices, 2000, Page 168 plus cover page and publication page, Rosamund M. Baird, et al., Editor, Taylor & Francis Publisher, USA and Canada.	☐
	2	HERRERO, VANRELL, R., "Preservatives in Ophthalmic Formulations: An Overview," Arch. Soc. Esp. Oftalmol, 2007, Vol. 82., pgs. 531-532.	☐
	3	JOHNSON, MALCOM, "Development of fluticasone propionate and comparison with other inhaled corticosteroids," J. Allergy Clin. Immunol., April 1998, Vol. 101, No. 4, Part 2, pgs. S434-S439.	☐

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

EXAMINER SIGNATURE

Examiner Signature	/Thor Nielsen/	Date Considered	02/09/2011

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

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

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /T.N./

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	10518016
Filing Date	2005-07-06
First Named Inventor	Amar Lulla
Art Unit	1616
Examiner Name	Kristie Latrice Brooks
Attorney Docket Number	PAC/20632 US(4137-04700)

U.S.PATENTS Remove

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

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

U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20020076382	A1	2002-06-20	Kaplan, et al.	
	2	20040136918	A1	2004-07-15	Garrett, et al.	
	3	20090291143	A1	2009-11-26	Lulla, et al.	
	4	20090318397	A1	2009-12-24	Lulla, et al.	

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

FOREIGN PATENT DOCUMENTS Remove

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	10518016
	Filing Date	2005-07-06
	First Named Inventor	Amar Lulla
	Art Unit	1616
	Examiner Name	Kristie Latrice Brooks
	Attorney Docket Number	PAC/20632 US(4137-04700)

	1							☐

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

NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	Office Action dated September 30, 2010, Application Serial No. 12/508,388 filed on July 23, 2009, 22 pages.	☐
	2	Office Action dated September 30, 2010, Application Serial No. 12/508,393 filed on July 23, 2009, 31 pages.	☐
	3	SCHMIDT, M. W., "The new topical steroid ciclesonide is effective in the treatment of allergic rhinitis," Journal of Clinical Pharmacology, 1999, vol. 39, pgs. 1062-1069.	☐
	4	Patent application entitled "Combination of azelastine and steroids," by Amar Lulla, et al., filed September 10, 2010 as serial number 12/879,515.	☐

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

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

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

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	10518016
	Filing Date	2005-07-06
	First Named Inventor	Amar Lulla
	Art Unit	1616
	Examiner Name	Kristie Latrice Brooks
	Attorney Docket Number	PAC/20632 US(4137-04700)

CERTIFICATION STATEMENT

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

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

OR

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

☐ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ None

SIGNATURE

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

Signature	/Rodney B. Carroll/	Date (YYYY-MM-DD)	2010-10-19
Name/Print	Rodney B. Carroll	Registration Number	39,624

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

Privacy Act Statement

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

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

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

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

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

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

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

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

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

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

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

Electronic Acknowledgement Receipt

EFS ID:	8655538
Application Number:	10518016
International Application Number:	
Confirmation Number:	4912
Title of Invention:	Combination of azelastine and steroids
First Named Inventor/Applicant Name:	Amar Lulla
Customer Number:	30652
Filer:	Rodney B. Carroll/Linda Kerrick
Filer Authorized By:	Rodney B. Carroll
Attorney Docket Number:	PAC/20632 US (4137-04700)
Receipt Date:	19-OCT-2010
Filing Date:	06-JUL-2005
Time Stamp:	18:14:40
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	NPL Documents	093010_OA_12508388.pdf	515248 29ffb06b2911c950ead5844d6e5fcb6f3f90a7	no	22

Warnings:	
Information:	000533

2	NPL Documents	093010_OA_12508393.pdf	1698566 82203ddfbcd450134f1f448d79b8486d63c0c99f	no	31
Warnings:					
Information:					
3	NPL Documents	SCHMIDT_TheNewTopical.pdf	1167967 9e1ebb36482fc3fb9e67a178ac0907b3e9ffed2f	no	8
Warnings:					
Information:					
4	Information Disclosure Statement (IDS) Filed (SB/08)	101910_IDS.pdf	804274 ee6a1441986ba712f948b7b7e2fef96bafb2ae0e	no	4
Warnings:					
Information:					
		Total Files Size (in bytes):	4186055		

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

Doc code: RCEX
Doc description: Request for Continued Examination (RCE)

PTO/SB/30EFS (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)

Application Number	10518016	Filing Date	2005-07-06	Docket Number (if applicable)	PAC/20632 US(4137-04700)	Art Unit	1616
First Named Inventor	Amar Lulla			Examiner Name	Kristie Latrice Brooks		

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV

SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☒ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____

☒ Other Information Disclosure Statement submitted September 24, 2010.

☐ Enclosed

☐ Amendment/Reply

☐ Information Disclosure Statement (IDS)

☐ Affidavit(s)/ Declaration(s)

☐ Other _____

MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____ (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

FEES

The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.

☒ The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 501515

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature

☐ Applicant Signature

PTO/SB/30EFS (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Signature of Registered U.S. Patent Practitioner			
Signature	/Rodney B. Carroll/	Date (YYYY-MM-DD)	2010-09-27
Name	Rodney B. Carroll	Registration Number	39624

This collection of information is required by 37 CFR 1.114. 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 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

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

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

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

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

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

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

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

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

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

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

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

Electronic Patent Application Fee Transmittal

Application Number:	10518016
Filing Date:	06-Jul-2005
Title of Invention:	Combination of azelastine and steroids
First Named Inventor/Applicant Name:	Amar Lulla
Filer:	Rodney B. Carroll/Linda Kerrick
Attorney Docket Number:	PAC/20632 US (4137-04700)

Filed as Large Entity

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

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

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Request for continued examination	1801	1	810	810
		Total in USD ($)		**810**

Electronic Acknowledgement Receipt

EFS ID:	8508698
Application Number:	10518016
International Application Number:	
Confirmation Number:	4912
Title of Invention:	Combination of azelastine and steroids
First Named Inventor/Applicant Name:	Amar Lulla
Customer Number:	30652
Filer:	Rodney B. Carroll/Linda Kerrick
Filer Authorized By:	Rodney B. Carroll
Attorney Docket Number:	PAC/20632 US (4137-04700)
Receipt Date:	27-SEP-2010
Filing Date:	06-JUL-2005
Time Stamp:	20:04:29
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$810
RAM confirmation Number	6374
Deposit Account	501515
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
00001					

1	Request for Continued Examination (RCE)	092710_RCE.pdf	769878 8f4f72720a50df805c4c185cf01961ad6e8b8869	no	3
Warnings:					
Information:					
2	Fee Worksheet (PTO-875)	fee-info.pdf	30237 b42e929e0176e3ee88424493d1e53364c6c90865	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	800115	

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Amar Lulla, *et al.*	§	
		§	Group Art Unit: 1616
Serial No.:	10/518,016	§	
		§	Examiner: Kristie Latrice Brooks
Filed:	July 6, 2005	§	
		§	Confirmation No.: 4912
For:	COMBINATION OF AZELASTINE AND STEROIDS	§	
		§	
		§	

Mail Stop: After Final
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

CERTIFICATE OF EFS-WEB FILING

I hereby certify that this correspondence is being electronically filed at the USPTO website to: Mail Stop After Final, Commissioner for Patents, P.O. Box 1450, Alexandria VA 22313-1450 on Sept. 24, 2010

Linda Kerrick

Linda Kerrick

AMENDMENTS AND RESPONSE TO FINAL OFFICE ACTION DATED APRIL 28, 2010

Dear Sir:

In response to the Final Office Action dated April 28, 2010, Applicants respectfully request reconsideration of the above-identified application as follows.

A listing of claims begins on page 2 of this paper.

Remarks/Arguments begin on page 9 of this paper.

LISTING OF CLAIMS

1. (Previously Presented) A pharmaceutical formulation which comprises azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, and fluticasone or a pharmaceutically acceptable ester thereof, which contains the fluticasone or a pharmaceutically acceptable ester thereof in an amount from about 50 micrograms/ml to about 5 mg/ml of the formulation.

2. (Original) A pharmaceutical formulation according to claim 1, wherein said azelastine is present as azelastine hydrochloride.

3. (Canceled)

4. (Previously Presented) A formulation according to claim 1, wherein the pharmaceutically acceptable ester is fluticasone propionate or fluticasone valerate.

5. (Canceled)

6. (Previously Presented) A formulation according to claim 1, wherein the formulation has a particle size of less than 10 μm.

7. (Previously Presented) A formulation according to claim 1, which is a suspension containing 0.0005 to 2% (weight/weight of the formulation) of azelastine or a pharmaceutically

acceptable salt of azelastine, and from 0.5 to 1.5% (weight/weight of the formulation) of fluticasone or a pharmaceutically acceptable ester thereof.

8. (Previously Presented) A formulation according to claim 7, which contains from 0.001 to 1% (weight/weight of the formulation) azelastine, or salt thereof, and from 0.5% to 1.5% (weight/weight of the formulation) fluticasone or a pharmaceutically acceptable ester thereof.

9. (Previously Presented) A formulation according to claim 1, which also contains a surfactant.

10. (Original) A formulation according to claim 9, wherein the surfactant comprises a polysorbate or poloxamer surfactant.

11. (Previously Presented) A formulation according to claim 9, which contains from about 50 micrograms to about 1 milligram of surfactant per ml of the formulation.

12. (Previously Presented) A formulation according to claim 1, which also contains an isotonic agent.

13. (Original) A formulation according to claim 12, wherein the isotonic agent comprises sodium chloride, saccharose, glucose, glycerine, sorbitol or 1,2-propylene glycol.

14. (Previously Presented) A formulation according to claim 1, which also contains at least one

additive selected from the group consisting of a buffer, a preservative, a suspending agent and a thickening agent.

15. (Original) A formulation according to claim 14, wherein said preservative is selected from edetic acid and its alkali salts, lower alkyl p-hydroxybenzoates, chlorhexidine, phenyl mercury borate, or benzoic acid or a salt, a quaternary ammonium compound, or sorbic acid or a salt thereof.

16. (Previously Presented) A formulation according to claim 14, wherein the suspending agent or thickening agent is selected from cellulose derivatives, gelatin, polyvinylpyrrolidone, tragacanth, ethoxose (water soluble binding and thickening agents on the basis of ethyl cellulose), alginic acid, polyvinyl alcohol, polyacrylic acid, or pectin.

17. (Previously Presented) A formulation according to claim 14, wherein the buffer comprises a citric acid-citrate buffer.

18. (Previously Presented) A formulation according to claim 14, wherein the buffer maintains the pH of the aqueous phase at from 3 to 7.

19. (Previously Presented) A formulation according to claim 1, which is an aqueous suspension or solution.

20. (Previously Presented) A formulation according to claim 1, which is in the form of an

aerosol, an ointment, eye drops, nasal drops, a nasal spray, an inhalation solution and other forms suitable for nasal or ocular administration.

21. (Original) A formulation according to claim 20, which is in the form of nasal drops or nasal spray.

22. (Original) A formulation according to claim 20, which is in the form of an aerosol.

23-25. (Canceled)

26. (Currently Amended) A pharmaceutical product, comprising (i) azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, provided in an aerosol formulation ~~preferably~~ together with a propellant typically suitable for MDI delivery, and (ii) fluticasone or a pharmaceutically acceptable ester thereof, provided in an aerosol formulation ~~preferably~~ together with a propellant typically suitable for MDI delivery, as a combined preparation for ~~simultaneous, separate or sequential~~ use in the treatment of conditions for which administration of one or more anti-histamine and/or one or more steroid is indicated.

27. (Currently Amended) An aerosol formulation ~~preferably~~ suitable for MDI delivery comprising the formulation of claim 1, together with a propellant.

28-29. (Canceled)

30. (Currently Amended) A pharmaceutical product comprising the formulation according to claim 1, wherein (i) azelastine, or a pharmaceutically acceptable salt thereof, and (ii) fluticasone or a pharmaceutically acceptable ester thereof, as a combined preparation with said azelastine for ~~simultaneous, separate or sequential~~ use in the treatment of conditions for which administration of one or more anti-histamine and/or one or more steroid is indicated.

31-34. (Canceled)

35. (Previously Presented) A pharmaceutical product comprising the pharmaceutical formulation of claim 1, wherein said azelastine is azelastine hydrochloride and said pharmaceutically acceptable ester is fluticasone propionate, as a combined preparation for simultaneous, separate or sequential use in the treatment of conditions for which administration of one or more anti-histamine and/or one or more steroid is indicated.

36. (Previously Presented) A pharmaceutical formulation according to claim 1, wherein said azelastine is azelastine hydrochloride and said pharmaceutically acceptable ester is fluticasone propionate, together with a pharmaceutically acceptable carrier or excipient therefor.

37. (Previously Presented) A pharmaceutical product comprising the pharmaceutical formulation of claim 1, wherein said azelastine is azelastine hydrochloride and said pharmaceutically acceptable ester is fluticasone valerate, as a combined preparation for simultaneous, separate or sequential use in the treatment of conditions for which administration of one or more anti-histamine and/or one or more steroid is indicated.

38. (Previously Presented) A pharmaceutical formulation according to claim 1, wherein said azelastine is azelastine hydrochloride and said pharmaceutically acceptable ester is fluticasone valerate, together with a pharmaceutically acceptable carrier or excipient therefor.

39-43. (Canceled)

44. (Previously Presented) A process of preparing a pharmaceutical product according to claim 26, which process comprises providing (i) azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, and (ii) fluticasone or a pharmaceutically acceptable ester thereof, as a combined preparation for simultaneous, separate or sequential use in the treatment of conditions for which administration of one or more antihistamine and/or one or more steroid is indicated.

45. (Previously Presented) A process of preparing a pharmaceutical formulation according to claim 1, which process comprises admixing a pharmaceutically acceptable carrier or excipient with azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, and fluticasone or a pharmaceutically acceptable ester thereof.

46-52. (Canceled)

53. (Previously Presented) A formulation according to claim 1, wherein the pharmaceutically acceptable ester is fluticasone propionate.

54. (Previously Presented) A formulation according to claim 1, wherein the pharmaceutically acceptable ester is fluticasone valerate.

55. (Previously Presented) A pharmaceutical product comprising (i) azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, provided as a nasal spray, and (ii) fluticasone or a pharmaceutically acceptable ester thereof, provided as a nasal spray, as a combined preparation for simultaneous, separate or sequential use in the treatment of conditions for which administration of one or more anti-histamine and/or one or more steroid is indicated.

56. (Previously Presented) A nasal spray formulation comprising (i) azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, and (ii) fluticasone or a pharmaceutically acceptable ester thereof, together with a pharmaceutically acceptable carrier or excipient therefor.

REMARKS/ARGUMENTS

Status of Claims

Claims 26, 27, and 30 have been amended.

Claims 3, 5, 23-25, 28, 29, 31-34, 39-43, and 46-52 have been canceled.

Thus, claims 1, 2, 4, 6-22, 26, 27, 30, 35-38, 44-45, and 53-56 are currently pending in this application.

Applicants hereby request further examination and reconsideration of the presently claimed application.

Claim Amendments

Applicants have for the sake of clarity amended claims 26 and 27 to remove the term "preferably." Additionally, claims 26 and 30 have been amended to remove the phrase "simultaneous, separate or sequential." No new matter has been introduced as a result of these amendments.

Claim Rejections – 35 U.S.C. § 103

Claims 1-2, 4, 7-21, 30, 35-38, 44-45 and 53-56 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Cramer, EP 0780127 (hereinafter "*Cramer*").

Claims 22 and 26-27 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over *Cramer* in view of Modi, U.S. Patent No. 6,294,153 (hereinafter "*Modi*").

Claims 1-2 and 6 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over *Cramer* in view of Fassberg, et al., U.S. Patent No. 6,416,743 (hereinafter "*Fassberg*").

Claims 1, 25, and 28-29 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over *Cramer* in view of Alfonso, et al., U.S. Patent No. 6,017,963 (hereinafter "*Alfonso*").

Claims 25, 28, and 29 are currently canceled. Accordingly, the pending claims stand or fall on the above-recited application of the primary reference, *Cramer*, alone or in combination with the secondary references, *Modi* or *Alfonso*, to independent claims 1, 26, 55, and 56. Applicants respectfully submit the pending claims are patentable in view of the cited references and provide herewith objective evidence of nonobviousness in that the claimed species directed to a pharmaceutical formulation comprising azelastine and fluticasone displays unexpectedly beneficial properties, is commercially successful, and fills a long felt but unsolved need.

The Legal Standard for Obviousness

The MPEP provides that "establishing a *prima facie* case of obviousness" requires, "the clear articulation of the reason(s) why the claimed invention would have been obvious." *See* MPEP § 2142. The MPEP also acknowledges that "[t]he Supreme Court in *KSR* noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit." *See* MPEP § 2143.

Moreover, in *KSR Int'l Co. v. Teleflex, Inc.*, the United States Supreme Court explained that, "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art," but, additionally whether "the claim extends to what is obvious." *See KSR Int'l Co. v. Teleflex, Inc.*, 82 USPQ2d 1385, 1397 (2007). Expounding on its edict, the Supreme Court went on to opine that an obviousness determination is based upon a "proper application of *Graham*," including consideration of "secondary factors" that may weigh against an obviousness determination. *See KSR Int'l Co. v. Teleflex, Inc.*, 82 USPQ2d at 1399 (citing *Graham v. John Deere Co. of Kansas City, et al.*, 383 U.S. 1, 148 USPQ 459 (1966)). The Office Action states:

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

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

A. *Cramer* does not fairly suggest the elected species

In ascertaining the difference in the prior art and the pending claims, the Office Action dated January 23, 2009 (hereinafter *OA 01232009*) acknowledges "Cramer does not exemplify a composition comprising azelastine and fluticasone." *See OA 01232009* at 12. As such, the Office Action retreats to a "rationale-based" obviousness rejection based on the conclusion that:

> one of ordinary skill in the art would have been motivated to make a composition comprising azelastine and fluticasone because Cramer suggests that the combination of a gluccocortoid (i.e. fluticasone) and antihistamine (i.e. azelastine) provide improved relief of symptoms associated with seasonal or perennial allergic rhinoconjunctivitis.

See OA 01232009 at 12.

The Office Action then supports its "rationale-based" rejection by stating, "the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made **because the prior art is fairly suggestive of the claimed invention**." *See OA 01232009* at 13 (emphasis added). The present Office Action maintains this position asserting that "[i]t is well within the means for one of ordinary skill in the art to try the instant combination as there are a small number of actives to **choose** from." *See* Office Action at 15, emphasis added. The Office Action's remark suggests a reliance on the KSR ruling and is asserting that it would have been "obvious to try" the instantly claimed combination.

Applicants submit the Office Action's rationale fails as it improperly applies the "obvious to try" standard. In *Kubin*, the Federal Circuit recognized that KSR "resurrects this court's own wisdom in *In re* O'Farrell" and addressed the question of "when is an invention that was obvious to try nevertheless nonobvious?" *In re Kubin*, 561 F.3d 1351, 1359(Fed. Cir. 2009) (citing *In re O'Farrell*, 853 F. 2d 894, 903(Fed. Cir. 1988)). In *Kubin*, the court described a class of cases where 'obvious to try' was erroneously equated with obviousness under § 103 as

> what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art either gave no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.

See id, emphasis added. The court in *Kubin* made clear that "where a defendant merely throws metaphorical darts at a board filled with combinatorial prior art possibilities, courts should not succumb to hindsight claims of obviousness." *See id.*

Applicants contend that *Cramer* does not provide any guidance as to which of the number of combinations disclosed were critical or likely to be successful in producing the beneficial results disclosed by Applicants. Absent such guidance, the only disclosure of record regarding the beneficial properties associated with the combination of azelastine and fluticasone is that of the instant application. Such hindsight reconstruction of the instant invention traverses the mandate of MPEP § 2142 that "hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art." Based on the foregoing, Applicants respectfully submit that the Office Action does not present a *prima facie* case of obviousness with regard to the instant claims.

B. Secondary considerations indicate that the combination of azelastine and fluticasone is nonobviousness

Assuming, without conceding, that the Office Action's "rationale and motivation" discussion is sufficient, nevertheless, the Office Action's suggestion of a *prima facie* case of obviousness must fail because the unaddressed "secondary considerations" described below render the instant claims nonobvious. *See KSR Int'l Co. v. Teleflex, Inc.*, 82 USPQ2d at 1399. Applicants provide herewith a Rule 1.132 declaration of inventor Geena Malhotra and the accompanying Exhibits A-D setting forth evidence of the following secondary considerations of nonobviousness.

Exhibit A has been amended

Applicants draw the Examiner's attention to Exhibit A submitted herewith. Applicants present in Exhibit A values that are amended (as shown in redline) from those presented in the Exhibit A filed in response to Office Action dated July 23, 2009. The amended values represent clarifications and the remedying of typographical errors in the previously submitted data. These corrections/amendments do not have any impact on the arguments previously submitted during the prosecution of the application.

1. The combination of azelastine and fluticasone displays unexpected, beneficial results

A showing of unexpected results may rebut a *prima facie* case of obviousness, and is particularly applicable in the inherently unpredictable chemical arts where minor changes may yield substantially different results. *See e.g., In re Soni*, 34 USPQ2d 1684, 1687 (Fed. Cir. 1995). Exhibit A of the declaration demonstrates that the claimed pharmaceutical formulation comprising azelastine and fluticasone has unexpected and beneficial stability. As noted in paragraph 2 of the declaration:

> The results in Table II show that the individual active materials (e.g., azelastine.HCl, budesonide, and fluticasone propionate) have good stability, in that the impurity levels are fairly constant in all the tests. The results in Table II also show that the combination of azelastine and budesonide are relatively unstable, with varying, and high amounts of impurities developing during the tests. Surprisingly, the results for azelastine and fluticasone show good stability throughout the tests, as the amount of impurity remains constant and at a low level.

These tests demonstrate that there is a clear unexpected advantage in product stability in formulating azelastine with fluticasone rather than with other steroids such as budesonide. Improved product stability is extremely important in pharmaceutical compositions as is understood by those skilled in the art.

Furthermore, Exhibits B1 and B3 of the declaration demonstrate that a pharmaceutical formulation comprising azelastine and fluticasone has unexpected and beneficial efficacy when administered to patients. Specifically, Exhibit B1 notes that the use of DUONASE (a commercial pharmaceutical formulation comprising azelastine and fluticasone) "is very effective when compared [to] the available other nasal sprays." Likewise, Exhibit B3 notes (with emphasis added):

> DUONASE Nasal Spray is very very effective in all types of allergic rhinitis. Especially in "Seasonal allergic rhinitis", Fluticasone alone or azelastine alone also has been tried. But single drug was not effective as compared with the combination of both i.e. "DUONASE Nasal Spray".

Likewise, the remainder of the doctor statements in Exhibit B extol the therapeutic benefits of the claimed pharmaceutical formulation comprising azelastine and fluticasone. Such recognition by skilled artisans of the merits of the invention is further evidence of nonobviousness. *See Akzo N.V. v. United States Int'l Trade Comm'n*, 1 USPQ2d 1241, 1247 (Fed. Cir. 1986). These doctor statements demonstrate a clear, unexpected advantage in treatment efficacy, namely that the combination of azelastine and fluticasone provides a synergistic benefit in efficacy over azelastine alone or fluticasone alone.

As set forth above, the declaration provides strong evidence that the claimed pharmaceutical formulation comprising azelastine and fluticasone has unexpected and beneficial stability, and that upon administration to a patient, unexpected and beneficial enhanced efficacy is observed. Accordingly, the claimed pharmaceutical formulation comprising azelastine and fluticasone is nonobvious in view of these unexpected results.

Response to alleged deficiencies of 1.132 Declaration

The Office Action asserts four alleged deficiencies of the previously submitted inventor declaration. *See* Office Action at 15 and 16. Without conceding that such deficiencies are present in the aforementioned declaration, Applicants will proceed to address these allegations in an effort to substantively advance prosecution of the instant application.

The Office Action first alleges there is no description of the testing method, assay utilized or how the impurity level was calculated. *See id.* Applicants provide herewith Exhibit D which describes the HPLC methodologies utilized for obtaining the stability data reported in Exhibit A. Particularly, Exhibit D provides conditions for HPLC analysis of the compositions discussed in Exhibit A and spectrophotometric detection of the indicated materials. Secondly, Exhibit D also identifies the nature of the impurities monitored for each composition. Applicants respectfully submit Exhibit D remedies the alleged deficiencies described in the Office Action with regard to Exhibit A and request reconsideration of the experimental showings provided in Exhibit A which support the nonobviousness of the claimed subject matter.

Thirdly, the Office Action's asserts that "Applicant did not test against the closest prior art examples described in *Cramer* (see Example 3). Example 3 in *Cramer* discloses a composition comprising azelastine and triamcinolone." *See* Office Action at 16. However, Applicants note that *Cramer* specifically treats fluticasone and budesonide as alternatives. *See Cramer*, claim 3. In

view of the teachings of the Office Action's cited reference, *Cramer*, the ordinarily skilled artisan would consider the appropriate comparatives to be that of azelastine and fluticasone to azelastine and budesonide. Applicants respectfully submit that such comparatives which are made in the aforementioned declaration are both appropriate and convincing as to the beneficial features associated with the azelastine/fluticasone composition.

Fourth and finally, Applicants note the Office Action's remarks with regard to the compositions described in Exhibit A that contain fluticasone also contain phenyl ethyl alcohol, a preservative/antibacterial. Particularly, the Office Action contends

> It is neither unexpected nor surprising that a composition comprising an additional preservative would be capable of keeping impurity levels lower and increasing shelf life when compared to a composition that does not contain the preservative or a lesser amount of the preservative.

See Office Action at 16-17. Applicants submit that the Office Action's analysis of the experimental results presented in Exhibit A is incomplete. Attention is respectfully directed to Exhibit A, Table 2 wherein the comparative stability of azelastine, budesonide, and fluticasone is presented. Budesonide in the absence of phenyl ethyl alcohol displays a total impurity level ranging from 0.25 to 0.49 over the course of the stability study. Fluticasone *in the presence of phenyl ethyl alcohol* over the course of the stability study displayed a range in the impurity level of from 0.46 to 0.53. Azelastine in the absence of phenyl ethyl alcohol shows a range in the impurity level over the course of the stability study of from 0.03 to 0.18. The ordinarily skilled artisan would surmise based on the information presented in Exhibit A that azelastine, fluticasone and budesonide independently exhibited similar stabilities over the course of the stability study. The presence of phenyl ethyl alcohol did not serve to distinguish the stability of the fluticasone sample from that of the azelastine or budesonide samples. To the contrary, budesonide samples and

azelastine samples in the absence of phenyl ethyl alcohol have a stability similar to that of fluticasone samples which contain phenyl ethyl alcohol. Applicants submit that the presence of phenyl ethyl alcohol in the azelastine and fluticasone composition cannot account for the observed dramatic increase in stability of this composition when compared to the azelastine and budesonide composition.

Further, Applicants provide herewith excerpts from the Handbook of Microbiological Quality Control and an article entitled "Preservatives in Ophthalmic Formulations." According to both these references, preservatives act on micro-organisms and help in protecting the formulation from them. None of these references mention the effect of preservatives on the chemical stability of the actives or drug. Thus, it is simply the assumption of the Office Action that the preservative *may* have an effect on the chemical stability of the actives.

The Office Action also makes statements that addition of a preservative prevents the decomposition of a substance or inhibits the multiplication of organisms which also causes decomposition. *See* Office Action at 15. The Office Action then refers the Applicants to two general references regarding the use of preservatives and cites a passage in *Cramer* regarding preservatives. However, the Office Action fails to establish that the microorganisms whose growth are inhibited by phenyl ethyl alcohol inherently impact the stability of azelastine and/or fluticasone but rather that such organisms *may* impact the stability of these materials. The fact that a certain result or characteristic **may** occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art) (emphasis added); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To

establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is **necessarily present** in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (emphasis added). As the Office Action has failed to establish that microorganisms inhibited by the presence of phenyl ethyl alcohol *necessarily* affect the stability of azelastine and/or fluticasone, Applicants respectfully assert that the submitted experimental showings would lead one of ordinary skill in the art to conclude the azelastine and fluticasone composition displays an unexpectedly beneficial stability when compared to the azelastine and budesonide composition. *See Inventor Declaration at 6.*

2. The combination of azelastine and fluticasone is commercially successful

Commercial success is a strong factor favoring nonobviousness. *See e.g., Akzo N.V.* at 1246. As noted in paragraph 4 of the declaration, a pharmaceutical formulation comprising azelastine and fluticasone is commercially available where approved as DUONASE nasal spray. The doctor statements set forth in Exhibit B provide further evidence of the commercial success of DUONASE nasal spray. Furthermore, as noted in paragraph 8 of the declaration the present application claiming a pharmaceutical formulation comprising azelastine and fluticasonse is licensed to Meda Pharmaceuticals, which specializes in respiratory, allergy, and cough-cold products. Given its expertise and knowledge in the field of treatment, the willingness of Meda Pharmaceuticals to license the pending application is further evidence of the commercial success of the claimed pharmaceutical formulation comprising azelastine and fluticasone. Accordingly, the claimed pharmaceutical formulation comprising azelastine and fluticasone is nonobvious in view of its commercial success.

3. The combination of azelastine and fluticasone fills a long-felt need

As set forth in *Graham*, the existence of a long-felt and unsolved need in the art is further evidence of nonobviousness. Applicants note that *Cramer* was published on June 25, 1997, which was over 10 years ago. Nonetheless, as noted in paragraph 7 of the declaration, inventor Geena Malhotra is unaware of another commercially available pharmaceutical formulation comprising an antihistamine and a steroid. Likewise, the doctor statement of Exhibit B4 notes that:

> I have been using nasal sprays from the year 1993, ever since I joined my present institution. I have used Beclomethasone, Budesonide, Azelastine, Fluticasone, Mometasone, with oral antihistamines down the line till date.
>
> The present combination spray of a weak (non sedating component) Azelastine and fluticasone (steroid component) is complete by itself in my patients of chronic simple rhinitis following nasal + sinus polyposis surgery and those unwilling for surgery or unfit for surgery.

Such "[f]irsthand practical knowledge of unsolved needs in the art, by an expert, is evidence of the state of the art." *See In re Piasecki*, 223 USPQ 785, 789 (Fed. Cir. 1984). Applicants respectfully submit that the evidence establishes a long-felt need dating back to 1993 that continued unsolved even after the subsequent publication of *Cramer* in 1997. Applicants further submit that the lack of another commercially available pharmaceutical formulation comprising an antihistamine and a steroid further evidences a long-felt need and the failure of others to address the need prior to the present invention. Accordingly, the claimed pharmaceutical formulation comprising azelastine and fluticasone is nonobvious given that it meets the long-felt need outlined above.

4. The secondary considerations require a finding of nonobviousness

As set forth above, the claimed pharmaceutical formulation comprising azelastine and fluticasone displays unexpected, beneficial results; is commercially successful; and fills a long-felt need in the art. Accordingly, the totality of the secondary considerations requires a finding that the pending claims are not obvious, and therefore patentable, in view of the prior art of record.

CONCLUSION

Consideration of the foregoing amendments and remarks, reconsideration of the application, and withdrawal of the rejections are respectfully requested by Applicants. No new matter is introduced by way of the amendment. It is believed that each ground of rejection raised in the Final Office Action dated April 28, 2010 has been fully addressed. If any fee is due as a result of the filing of this paper, please appropriately charge such fee to Deposit Account Number 50-1515 of Conley Rose, P.C., Texas. If a petition for extension of time is necessary in order for this paper to be deemed timely filed, please consider this a petition therefore.

If a telephone conference would facilitate the resolution of any issue or expedite the prosecution of the application, the Examiner is invited to telephone the undersigned at the telephone number given below.

Respectfully submitted,
CONLEY ROSE, P.C.

Date: 9-24-10

Rodney B. Carroll
Reg. No. 39,624

ATTORNEY FOR APPLICANTS

5601 Granite Parkway, Suite 750
Plano, Texas 75024
(972) 731-2288 (Telephone)
(972) 731-2289 (Facsimile)

Handbook of Microbiological Quality Control

Pharmaceuticals and Medical Devices

Edited by

ROSAMUND M.BAIRD

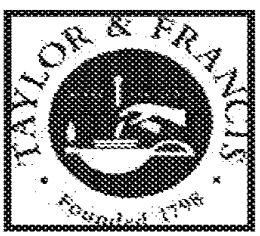
Department of Pharmacy and Pharmacology, University of Bath, UK

NORMAN A.HODGES

School of Pharmacy and Biomolecular Sciences, University of Brighton, UK

STEPHEN P.DENYER

School of Pharmacy and Biomolecular Sciences, University of Brighton, UK



First published 2000 by Taylor & Francis
11 New Fetter Lane, London EC4P 4EE

Simultaneously published in the USA and Canada
by Taylor & Francis Inc,
29 West 35th Street, New York, NY 10001

Taylor & Francis is an imprint of the Taylor & Francis Group

Typeset in Times by Keyword Publishing Services Ltd
Printed and bound in Great Britain by TJ International Ltd, Padstow

British Library Cataloguing in Publication Data
A catalogue record for this book is available from the British Library

Library of Congress Cataloging in Publication Data
Handbook of microbiological quality control: pharmaceuticals and medical devices/
edited by Stephen Denyer, Rosamund M.Baird, Norman A.Hodges.
p. cm.—(Taylor & Francis series in pharmaceutical sciences)
Includes bibliographical references and index.
1. Pharmaceutical microbiology-Handbooks, manuals, etc. 2.
Drugs—Sterilization—Handbooks, manuals, etc. 3. Pharmaceutical industry—Quality control—Handbooks, Manuals, etc. I. Denyer, Stephen (Stephen Paul) II, Baird, R.M. (Rosamund M.) III. Hodges, Norman A. IV. Series.

QR46.5. H36 2000
615′.19–dc21 00–041187

ISBN 0-748-40614-X

10

Antimicrobial Preservative Efficacy Testing

NORMAN HODGES AND GEOFFREY HANLON

School of Pharmacy and Biomolecular Sciences, Brighton University, BN2 4GJ, United Kingdom

10.1 Introduction

A wide variety of products need to be protected from attack by micro-organisms during their period of use. This is both to protect the user from the dangers of infection and to prevent spoilage and deterioration of the product. In the case of medicines, foods and cosmetics, the safety of the user is the main priority, but maintenance of product quality and appearance and suitability of the product for its intended purpose are also important.

Preservatives are intended to protect the product from spoilage due to organisms introduced by the user and those which unavoidably arise during the manufacturing process; preservatives should never be used to counter poor manufacturing procedures or poor-quality ingredients. Clearly, sterile products in single dose units do not require preservation, neither do non-sterile single dose units such as tablets and capsules which are unlikely to sustain microbial survival provided that they are contained within suitable packaging. The need for a preservative system, therefore, most commonly arises if the product is to be subject to microbial challenge during repeated use. Some products are self-preserving, either because the active ingredients are inhibitory, the pH is inimical to growth, or because they contain high concentrations of sugar or other solutes which act as osmotic preservatives. These types of formulations are rare in the pharmaceutical arena, and the majority of multi-dose water-containing medicines incorporate chemical preservatives to prevent microbial spoilage.

The term preservative describes the *function* of a chemical agent in protecting a product from degradation or change which might arise if micro-organisms were to gain access and grow in it. However, this can be misleading since it might be thought that preservatives merely maintain the *status quo* (prevent micro-organisms growing, but not necessarily kill them), and as a result it is not uncommon to encounter the phrase *preservative levels of biocide* implying low concentrations of chemical agents which have only a bacteriostatic effect. In the majority of cases, however, the concentrations of preservatives used in product formulations are designed to give a rapid kill of any invading micro-organisms. Increasingly, preservatives are used in

PRESERVATIVES IN OPHTHALMIC FORMULATIONS: AN OVERVIEW

GENERALIDADES DE LOS CONSERVANTES EN LAS FORMULACIONES OFTÁLMICAS

HERRERO VANRELL R[1]

In certain ocular pathologies, ophthalmic formulations need to be chronically administered in order to guarantee their efficacy. Typical examples of such pathologies are dry eye and glaucoma. Nevertheless, although preservatives have been frequently used in eye drops, its frequent use has been associated with alterations in the precorneal film, while in patients suffering from dry eye they tend to aggravate the already existing problem. On the other hand, in glaucoma patients the prolonged use of eye drops with preservatives has been associated with changes in the ocular surface accompanied by inflammation. In fact, conjunctival byopsies in patients suffering from glaucoma have revealed an increased number of immune cells and fiberblasts (1,2).

Thanks to the experience garnered so far, we can say that the successive administration of formulations with preservatives has a toxic effect in the ocular surface and in particular in those patients whose surface is compromised. However, as stated by the Real Farmacopea Española (RFE), the use of preservatives is mandatory in the case of multidose formulations, since bacterial contamination takes place when handling containers twice a day for two weeks. As quoted by the RFE (3): *Aqueous formulations in multidose containers shall include the appropriate antimicrobial preservative at adequate concentrations in order to prevent tampering of preparations during the time of use, except in those instances when preparations feature sufficient antimicrobial properties.*

A wide number of preservatives is used in the formulation of eye drops, among them benzalkonium chloride, benzethonium chloride and cetyl pyridinium chloride, benzyl bromide, EDTA, phenylmercury nitrate, phenylmercury acetate, thimerosal, merthiolate, acetate and phenylmercury borate, polymyxin B sulphate, chlorhexidine, methyl and propyl parabens, phenylethyl alcohol, quaternary ammonium chloride, sodium benzoate, sodium propionate and sorbic acid.

Progress in the treatment of dry eye has been linked to the emergence of new preservatives in the market based on stabilized chloride and oxygen compounds (Purite®) as well as sodium perborate (4). These agents have raised enormous interest since they were effective and apparently did not entail epithelial damage as other conventional drugs did. In any case, one of the most significant advances in the treatment of dry eye was the development of preservative-free artificial tears in monodose containers or else the inclusion of a sterilizing filter in multidose containers (Sistema Abak®).

The action mechanism of preservatives may be divided into two main categories: surfactants and oxidants (1,2).

Surfactants act upon microorganisms altering the cellular membrane and resulting in the lysis of the cytoplasm content. Cells in mammals cannot neutralize chemical preservatives, and thus preservatives become part of the cell and results in toxic effects. The classical example for this type of agents is benzalkonium chloride.

Oxidizing preservatives are usually smaller molecules interfering with cell functions. They may destabilize membranes, although to a lesser extent than chemical agents may. They are less toxic for mammal cells, which are equipped with enzymes capable of catalyzing the decomposition of hydrogen peroxide as long as preservatives are found in

[1] Dept. of Pharmacy and Pharmaceutical Technology. Pharmacy College. Complutense University. 28040 Madrid.
E-mail: rociohv@farm.ucm.es

low concentrations. Stabilized chlorine and oxygen compounds and sodium perborate are some examples of oxidizing preservatives.

Taking into account their impact on the corneal epithelium, it is clear that preservatives should not be used when there is some kind of trauma or in patients who have undergone a surgical procedure, since there is a risk of causing irritation in the anterior chamber. We need to take into consideration the fact that these agents are exclusively devoted to preventing the potential contamination of solutions by microorganisms during the use of this medication and should not to be included in formulations for intraocular use.

Another relevant aspect to take into account is that the intermittent use of formulations with preservatives needs not to be theoretically linked to adverse side effects. However, the use of several eye drops at the same time increases exposure to preservatives, since the concentration to which the ocular surface is exposed increases together with the number of applications. Furthermore, repeated doses may result in the accumulation of preservatives.

Obviously, the use of preservatives in ophthalmic formulations is necessary and cannot be avoided. Nevertheless, we should determine which preservatives induce less toxicity in epithelial and conjunctival cells. Cellular lines and cellular feasibility trials are efficient tools to bring about these studies.

REFERENCES

1. *Noecker R. Ophthalmic preservatives: considerations for long-term use in patients with dry eye or glaucoma. Rev Ophthalmol 2001; 8: 73-79.*
2. *Noecker R. Effects of common ophthalmic preservatives on ocular health. Adv Ther 2001; 18: 205-215.*
3. *Real Farmacopea Española. III ed. Madrid: Ministerio de Sanidad y Consumo; 2007.*
4. *Bartlett JD. Ophthalmic Drug Facts. St. Louis: Wolters Kluwer Health Inc; 2006.*
5. *United States Pharmacopeia Convention. USP 30. NF 25. The United States Pharmacopeial. The National Formulary. Rockville: 2007.*

Development of fluticasone propionate and comparison with other inhaled corticosteroids

Malcolm Johnson, PhD *Middlesex, United Kingdom*

Fluticasone propionate (FP) is a trifluorinated glucocorticoid based on the androstane nucleus. It was selected for development from structure-activity relationships (topical anti-inflammatory, cutaneous vasoconstriction, and hypothalamic-pituitary-adrenal axis suppression) of a series of 17β-carbothioates. FP is 3-, 300-, and 1000-fold more lipophilic than beclomethasone dipropionate, budesonide, and triamcinolone acetonide, respectively. FP has an absolute affinity (K_D) for the glucocorticoid receptor of 0.5 nmol/L and a relative receptor affinity 1.5-fold higher than beclomethasone-17-monopropionate (17-BMP) and mometasone furoate, 3-fold higher than budesonide, and 20-fold higher than flunisolide and triamcinolone acetonide. The rate of association of FP with the receptor is faster and the rate of dissociation slower than other corticosteroids. The resulting half-life of the FP active steroid-receptor complex is >10 hours, compared with approximately 5, 7.5, and 4 hours for budesonide, 17-BMP, and triamcinolone acetonide, respectively. FP has high selectivity for the glucocorticoid receptor, with little or no activity at other steroid receptors. FP is more potent than beclomethasone dipropionate, budesonide, triamcinolone acetonide, and mometasone furoate in inhibiting human T-cell migration and proliferation, inhibiting CD4+ T-cell cytokine and basophil histamine release, attenuating adhesion molecule expression, stimulating inflammatory cell apoptosis, and inducing cellular antiprotease release. In asthma patients, FP decreases the number of CD3+, CD4+, CD8+, and CD25+ T cells, mast cells, and eosinophils in bronchial biopsies, in addition to suppressing CD1a-dendritic and IgE+ cells and HLA-DR. FP, therefore, has a good pharmacologic profile for a topical steroid with increased intrinsic glucocorticoid potency and potent anti-inflammatory activity.
(J Allergy Clin Immunol 1998;101:S434-9.)

Key words: *Fluticasone propionate, inhaled corticosteroids, structure-activity relationships, asthma*

Abbreviations used

BDP:	Beclomethasone dipropionate
17-BMP:	Beclomethasone-17-monopropionate
FP:	Fluticasone propionate
GR:	Glucocorticoid receptor
GRE:	Glucocorticoid-responsive element
RBA:	Relative receptor binding affinity

To exert anti-inflammatory activity, a corticosteroid molecule must penetrate the cellular membrane and demonstrate affinity for the steroid binding site on the glucocorticoid receptor (GR), leading to activation of the receptor.[1] Dimerization of the active steroid-receptor complex occurs, and this can then enter the nucleus, bind to glucocorticoid-responsive elements on a target gene, influence gene transcription, and either inhibit proinflammatory or potentiate endogenous anti-inflammatory mechanisms. Alternatively, a direct interaction of the GR complex with transcription factors may also be an important determinant of steroid action and a key mechanism by which glucocorticoids exert some anti-inflammatory activity.[1]

The early development of corticosteroids based on the structure of cortisol focused on increasing topical potency and improving glucocorticoid selectivity. The first structure-activity studies attempted to find compounds with greater anti-inflammatory activity. This was achieved either by the insertion of an additional double bond at the 1,2 position in the steroid nucleus; by the introduction of 6α-fluoro, 6α-methyl, or 9α-fluoro substituents; or by a combination of these changes (Fig. 1). Although anti-inflammatory potency was potentiated, mineralocorticoid activity was increased to an even greater extent.[2] This effect was counteracted by further substitutions with α-hydroxyl, α-methyl, or β-methyl at the 16 position, for example, in dexamethasone (Fig. 1). A novel finding was that an ester function at the 16α, 17α, or 21α hydroxyl group was preferred, and this gave rise to betamethasone 17-valerate, triamcinolone 16,17-acetonide, and beclomethasone-17,21-dipropionate.[2] These compounds have proved to be of value in the treatment of the inflammatory component of bronchial asthma and rhinitis and have shown little detectable systemic activity when delivered by the topical route. However, concern that long-term therapy may result in a wide range of unacceptable systemic side effects such as adrenal suppression, bone fracture, osteoporosis, and inhibition of growth in children highlighted the need for steroids with a better therapeutic index.

DEVELOPMENT OF FLUTICASONE PROPIONATE

The development of fluticasone propionate was an attempt to produce a potent corticosteroid that exhibited improved airway selectivity (Table I) compared with earlier compounds. Lipophilicity was identified as an important physicochemical property for increased uptake and retention in lung tissue, resulting in enhanced lung-systemic distribution and greater affinity for the

From International Medical Affairs, Respiratory, Glaxo Wellcome Research and Development, Middlesex, United Kingdom.
Reprint requests: Malcolm Johnson, PhD, International Medical Affairs, Respiratory, Glaxo Wellcome Research and Development, Stockley Park West, Uxbridge, Middlesex, UK, UB11 1BT.

0091-6749/98 $5.00 + 0 **1/0/86611**

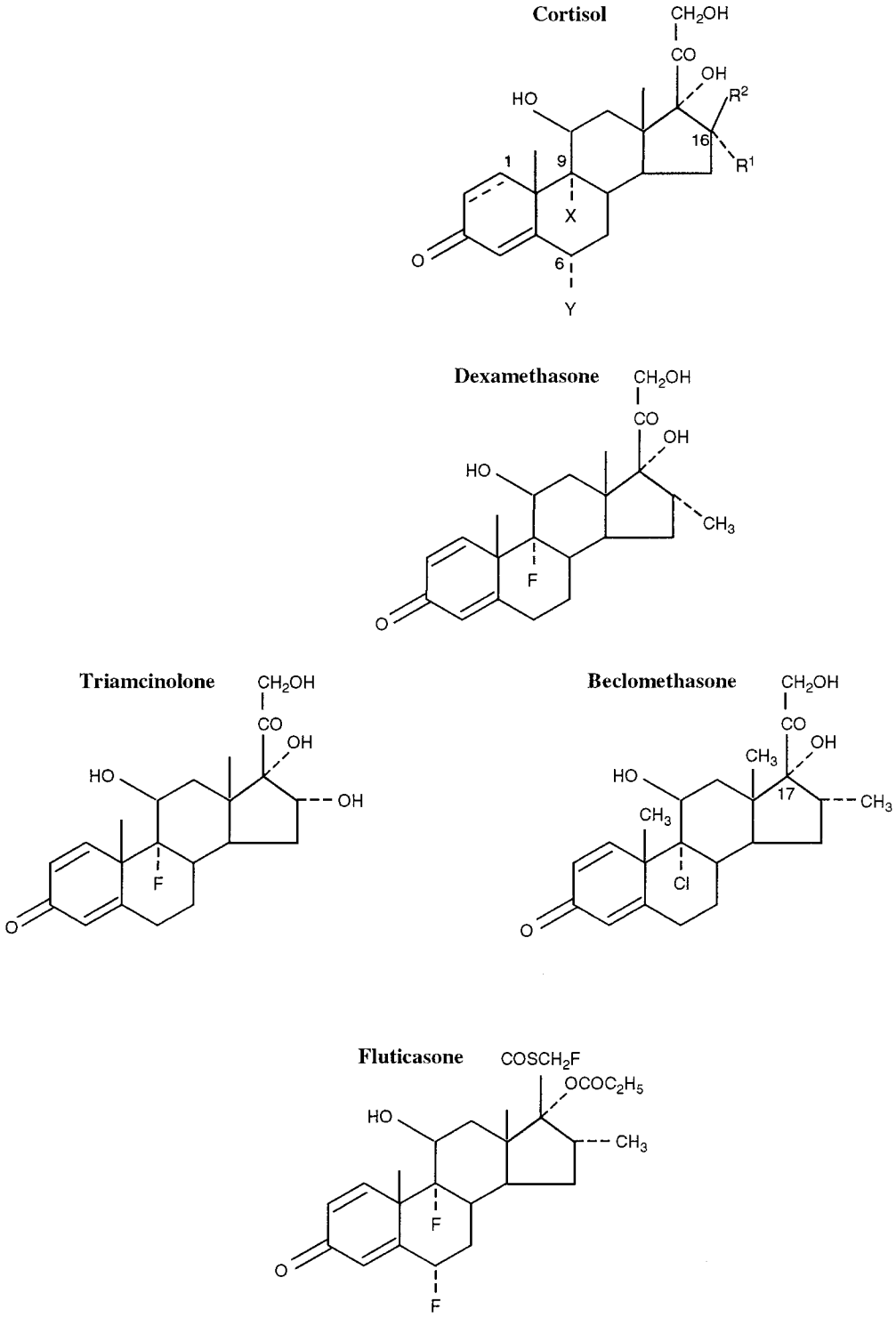


FIG. 1. Structural modifications of cortisol that produced the corticosteroids: dexamethasone, triamcinolone acetonide, beclomethasone dipropionate, and fluticasone propionate.

GR. The androstane nucleus, which is highly lipophilic, was therefore selected as the basis of the chemical program.[3] Topical activity was assessed by inhibition of croton oil–induced inflammation of the ear in a mouse model[4] and inhibitory activity at the hypothalamic-pituitary-adrenal (HPA) axis assessed by measuring reductions in circulating corticosteroids in response to ether stress.[5] The vasoconstriction/skin blanching assay[6]

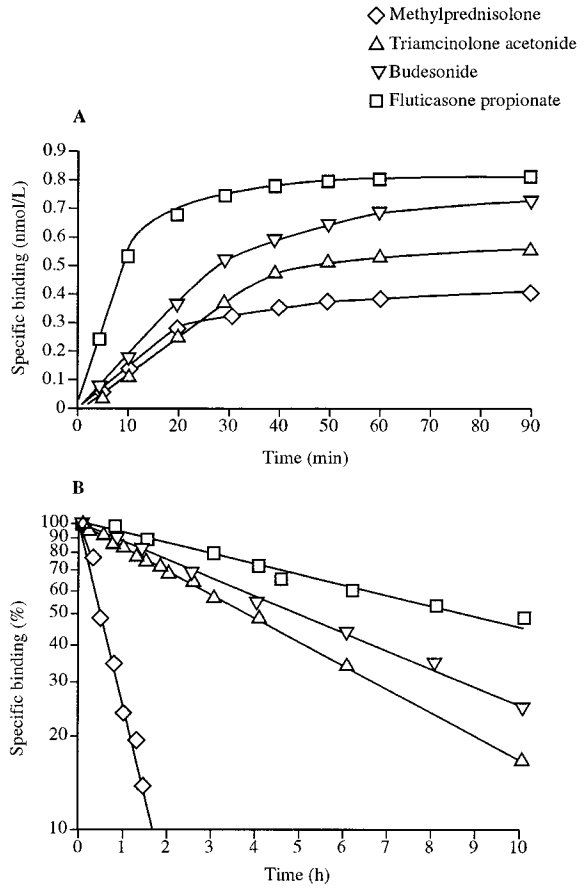


FIG. 2. Kinetics of **(A)** association and **(B)** dissociation of methylprednisolone, triamcinolone acetonide, budesonide, and fluticasone propionate with the glucocorticoid receptor in human lung tissue. Data from references 10 and 14.

was then used to confirm activity in human beings and to rank compounds in order of anti-inflammatory potency.

The androstane 17β-carboxylates, which lack the normal two-carbon side-chain of anti-inflammatory corticosteroids at the 17 position, were of particular interest.[3] The 17α-hydroxyl,17β-carboxylic acid was without activity in the vasoconstriction assay, with esterification being necessary for topical activity. Enzymatic hydrolysis of either ester function, which can occur in vivo, would therefore lead to inactive metabolites. The 17β-carboxylate series was superseded by the corresponding 17β-carbothioates.[3] Fluoromethyl analogues were, in general, more active than the corresponding chloromethyl compounds, with the 17-propionate being preferred over the acetate or butyrate; in addition, the presence of an α-CH_3 at position 16 reduced HPA axis–suppressing activity (Table II). The most active compound in the anti-inflammatory and vasoconstriction tests was the 6α,9α-difluoro, 17α-propionyl, 17β-carbothioate (fluticasone propionate), which was approximately 2-fold and 10-fold more potent than BDP and fluocinolone acetonide, respectively (Table II). Its low activity in inhibiting HPA axis function resulted from FP undergoing complete first-pass metabolism in the liver to the inactive 17β-carboxylic acid. X-ray crystallography has shown that the carbonyl of the 17β-substituent lies below the plane of the ring rather than above it, which is observed for other anti-inflammatory steroids.[7] This unusual shape, in which the carbothioate ester has increased accessibility, may explain why FP readily undergoes enzymatic hydrolysis. FP therefore has a high calculated therapeutic index (anti-inflammatory potency/HPA inhibitory potency) of 91, compared with 0.4 and 1.0 for BDP and fluocinolone acetonide, respectively.[8]

TABLE I. Criteria for improved airway selectivity of corticosteroids

Pharmacodynamics
• High glucocorticoid receptor affinity
• Optimal glucocorticoid receptor kinetics
• High intrinsic steroid potency/high topical anti-inflammatory activity
• High glucocorticoid receptor specificity
Pharmacokinetics
• Low oral bioavailability
• Increased uptake/retention in lung tissue
• Rapid systemic clearance
• Extrapulmonary metabolism to inactive metabolite(s)
• High lung:systemic distribution ratio

FP is 3 and 300 times more lipophilic than BDP and budesonide, respectively, and >1000-fold more lipophilic than either flunisolide or triamcinolone acetonide.[9] This degree of lipophilicity gives FP increased deposition in lung tissue and a slower release from the lung lipid compartment. In human lung fragments and nasal tissue in vitro, uptake and retention of corticosteroids is in the rank order FP > BDP > 17-BMP > budesonide > flunisolide > hydrocortisone.[10, 11] In patients with asthma, after inhalation of a 1 mg dose, FP exhibits a lung:systemic distribution ratio of 70 to 100,[12] compared with previous reports of 7 to 10 for budesonide.[13]

RECEPTOR PHARMACOLOGY

FP has a high affinity for the human lung GR (0.5 nmol/L),[14] which is 1.5-fold higher than 17-BMP and mometasone furoate, 3-fold higher than budesonide, and 10-fold higher than triamcinolone acetonide and flunisolide (Table III). Unlike budesonide, which is a racemic mixture of 22R and 22S enantiomers, FP does not have a chiral center and therefore the measured affinity represents the affinity of the molecule and not the contribution of the individual enantiomers. In contrast to 17-BMP, the metabolite of BDP that has a relative receptor binding affinity (RBA) 5-fold higher than the parent molecule, budesonide, with an RBA of 7.8, undergoes a marked reduction in activity when metabolized to either 6-hydroxy-budesonide (RBA = 0.06) or 16-α-hydroxy-prednisolone (RBA = 0.03). The

TABLE II. Structure-activity of halomethyl-androstane-17β-carbothioate analogues

Z	Y	X	R	16	Topical anti-inflammatory activity*	HPA suppression†	Cutaneous vasoconstriction‡
F	H	CI	C_2H_5	H	20	100	916
F	H	F	C_2H_5	H	63	149	1984
F	F	CI	C_2H_5	αCH_3	56	0.04	124
F§	F	F	C_2H_5	αCH_3	113	1.0	945
F	F	F	CH_3	αCH_3	76	2.9	392
F	F	F	C_3H_7	αCH_3	55	0.7	299
F	F	F	C_2H_5	βCH_3	197	>100	1048

Results are expressed relative to fluocinolone acetonide as standard (100). Data from Reference 3.
*Assessed with the croton oil ear assay in mice.[4]
†Assessed with the ether stress assay in rodents.[5]
‡Assessed with the skin blanching test in human volunteers.[6]
§Structure of fluticasone propionate.

TABLE III. Comparison of corticosteroid-glucocorticoid receptor affinity in human lung and potency in the cutaneous vasoconstriction test

Corticosteroid	Relative glucocorticoid receptor affinity*	Relative vasoconstrictor activity†
Fluocinolone acetonide	1.0	1.0
Beclomethasone-17-monopropionate	3.3	2.0
Triamcinolone acetonide	0.5	0.4
Flunisolide	0.45	0.5
Mometasone furoate	3.3	3.0
Budesonide	2.5	1.5
Fluticasone propionate	5.0	5.0

Activities are quoted relative to fluocinolone acetonide as standard (1.0).
*Data from Reference 14.
†Data from Reference 6.

TABLE IV. Corticosteroid-induced inhibition of human inflammatory cells

Corticosteroid	IC_{50} (nmol/L)			
	T-cell IL-5 release*	T-cell proliferation†	Basophil histamine release‡	Eosinophil apoptosis§
Beclomethasone dipropionate	7.7	10.0	1.0	138.7
Triamcinolone acetonide	9.8	1.0	20.0	23.8
Budesonide	1.7	0.2	0.6	8.5
Mometasone furoate	0.3	. . .	0.3	. . .
Fluticasone propionate	0.2	0.05	0.03	1.7

*Data from Reference 19.
†Data from Reference 18.
‡Data from Reference 20.
§Data from Reference 21.

17β-carboxylic acid metabolite of FP has negligible pharmacologic activity, with an RBA <0.01 at the GR.[9] The rate of association of steroid with the cytosolic GR is fastest for FP, followed by budesonide, triamcinolone acetonide, and methyl prednisolone (Fig. 2). In contrast, the rate of dissociation of FP from the receptor complex is slower than that of budesonide, triamcinolone acetonide, dexamethasone, and methyl prednisolone (Fig. 2). These differences in GR kinetics for FP result in differences in the stability of the steroid-receptor complex, which mediates the biologic and therapeutic activity of glucocorticoids.[1] The half-life of the steroid-receptor complex for FP is >10 hours, compared with approximately 3.5, 4.0, 5.0, and 7.5 hours for flunisolide, triamcinolone acetonide, budesonide, and 17-BMP, respectively.[9] FP is highly selective for the GR with <0.001 of the relative potency at human androgen, estrogen, and mineralocorticoid receptors.[15] The selectivity ratio of FP for the GR over the progestagen receptor is 1430, compared with 267 and 237 for 17-BMP and budesonide, respectively.

ANTI-INFLAMMATORY ACTIVITY

The steroid receptor profile of FP imparts a high topical anti-inflammatory activity. The active FP-GR complex binds to the GRE on target genes (EC_{50} = 3 nmol/L) or interacts directly with activating protein-1 and/or nuclear factor-kB transcription factors (EC_{50} range 0.01 to 0.1 nmol/L) at significantly lower concentrations than either dexamethasone or budesonide.[16] This has a good correlation with the respective potency of FP in inhibiting GRE-dependent cytokine (IL-6, IL-8) synthesis (IC_{50} range 5 to 10 nmol/L) and non–GRE-dependent cytokines such as tumor necrosis factor-α (TNFα) and granulocyte-macrophage colony stimulating factor (IC_{50} range 0.01 to 0.1 nmol/L).

There is also a good correlation between the relative affinity of these corticosteroids for the GR and their relative potency in a number of intact inflammatory cell systems (Table IV). For example, FP is more potent than dexamethasone, BDP, and budesonide in inhibiting human T-cell migration[17] and proliferation,[18] with IC_{50}

values of 0.3, 5.9, 2.0, and 0.8 nmol/L. Similarly, anti–CD3/CD28-induced IL-5 and IL-4 secretion from CD4+ T cells is inhibited by corticosteroids, with a rank order of potency of FP > mometasone furoate > budesonide > BDP > triamcinolone acetonide.[19] FP inhibits anti–IgE-stimulated histamine release from human basophils with an IC_{50} of 0.03 nmol/L, compared with 0.3, 0.6, 1, and 20 nmol/L for mometasone furoate, budesonide, BDP, and triamcinolone acetonide, respectively.[20] Corticosteroids, in the presence of IL-5, induce concentration-dependent apoptosis of eosinophils, with FP (EC_{50} = 1.7 nmol/L) being 5 times more potent than budesonide and approximately 10 times more potent than triamcinolone acetonide and flunisolide.[21] FP is also potent in inhibiting cytokine-induced adhesion molecule expression. At 1 nmol/L, FP inhibits TNFα-stimulated E-selectin in human endothelial cells,[22] whereas 8-fold higher concentrations of budesonide are required for the same effect. At a concentration of 100 nmol/L, FP is more effective than budesonide or triamcinolone acetonide in inhibiting intracellular adhesion molecule-1 expression in airway epithelial cells.[23] Finally, Abbin ante-Nissen et al.[24] have shown that corticosteroids induce the synthesis of the antiprotease, secretory leukocyte protease inhibitor (SLPI), in human airway epithelial cells. FP is the most potent steroid in inducing SLPI, with an EC_{50} of 0.1 nmol/L compared with 1, 5, and 2 nmol/L for triamcinolone acetonide, methylprednisolone, and dexamethasone, respectively.

The rank order of affinity of corticosteroids at the GR and their anti-inflammatory potency in vivo are similar. In the McKenzie test, in which the cutaneous vasoconstrictor and skin blanching response is used to rank anti-inflammatory potency of topical corticosteroids,[6] FP is 1.5-, 2.5-, and 3-fold more potent than 17-BMP, mometasone furoate, and budesonide, respectively, and 10-fold more potent than triamcinolone acetonide and flunisolide (Table III). This is in agreement with Dahlberg et al.,[25] who had previously reported that the RBA predicts relative potency for inhibition of edema.

CLINICAL STUDIES

In patients with asthma, FP treatment (1 mg twice daily for 2 months) significantly reduced the numbers of mast cells (by 80.2%), eosinophils (by 93.6%), and T cells (CD3, CD4, CD8, CD25; mean reduction of 86.5%) in bronchial biopsy specimens.[26] Similarly, the presence of dendritic (CD1a), IgE+, and HLA-DR+ cells in the lamina propria was decreased after FP 1 mg daily for 3 months,[27] suggesting attenuation of antigen recognition, processing, and presentation. Finally, FP (500 μg twice daily for 8 weeks) results in a marked decrease in the bronchoalveolar lavage levels of metalloprotease and an increase in the concentration of the endogenous tissue inhibitor of metalloproteases (TIMPS),[28] both of which have been implicated in matrix protein deposition and basement membrane thickening. FP, therefore, has good activity against the chronic inflammatory component of bronchial asthma and may attenuate the degree of airway remodeling.

The development of FP has resulted in a corticosteroid molecule with increased intrinsic glucocorticoid potency and potent anti-inflammatory activity, coupled with improved airway selectivity.[29] FP is of considerable clinical importance in the treatment of asthma and rhinitis.

REFERENCES

1. Barnes PJ, Adcock IM. Anti-inflammatory actions of steroids: molecular mechanism. Trends Pharmacol Sci 1993;14:436-41.
2. Phillipps GH. Locally active corticosteroids: structure-activity relationships. In: Wilson L, Markes R, editor. Mechanisms of topical corticosteroid activity. London: Churchill Livingstone; 1976. p. 1-18.
3. Phillipps GH, Bailey EJ, Bain BM, Borella RA, Buckton JB, Clark JC, et al. Synthesis and structure-activity relationships in a series of anti-inflammatory corticosteroid analogues, halomethyl androstane-17β-carbothiates and 17β-carboselenoates. J Med Chem 1994;37: 3717-29.
4. Tonelli G, Thibault L, Ringler I. A bio-assay for the concomitant assessment of the antiphlogistic and thymolytic activities of topically applied corticoids. Endocrinology 1965;77:625-34.
5. Zenker N, Bernstein DE. The estimation of small amounts of corticosterone in rat plasma. J Biol Chem 1958;231:695-701.
6. McKenzie AW. Percutaneous absorption of steroids. Arch Dermatol 1962;86:611-4.
7. Weeks CM, Duax WL, Wolff ME. A comparison of the molecular structures of six corticosteroids. J Am Chem Soc 1973;95:2865-8.
8. Phillipps GH. Structure-activity relationships of topically active steroids: the selection of fluticasone propionate. Respir Med 1990; 84(suppl):19-23.
9. Johnson M. Pharmacodynamics and pharmacokinetics of inhaled glucocorticoids. J Allergy Clin Immunol 1996;97:169-76.
10. Högger P, Rawert L, Rohdewald P. Dissolution tissue binding and kinetics of receptor binding of inhaled glucocorticoids. Eur Respir J 1993;6:584s.
11. Högger P, Bonsmann U, Rohdewald P. Efflux of glucocorticoids from human lung tissue to human plasma in vitro. Eur Respir J 1994;7:382s.
12. Högger P, Esmailpour N, Rabe K, Heitmann U, Nakashima N, Rhodewald P. Distribution of inhaled fluticasone propionate between lung tissue and blood plasma in vivo. Eur Respir J 1995;8: 303S.
13. Van den Bosch JMM, Westermann CJJ, Aumann J, Edsbacker S, Tönneffon M, Selrous O. Relationship between lung tissue and blood plasma concentrations of inhaled budesonide. Biopharm Drug Dispos 1993;14:455-9.
14. Högger P, Rohdewald P. Binding kinetics of fluticasone propionate to the human glucocorticoid receptor. Steroids 1994;59:597-602.
15. Harding SM. The human pharmacology of fluticasone propionate. Respir Med 1990;84(suppl):25-9.
16. Adcock IM, Barnes PJ. Ligand-induced differentiation of glucocorticoid receptor transrepression and transactivation. In: Acute and chronic inflammation in the respiratory tract, International Respiratory Forum. Reading UK: Colwood Publications; 1996. p. 25.
17. Cruikshank W, Masterson J, Center D. Effects of fluticasone propionate on random and stimulated T cell migration. In: Acute and chronic inflammation in the respiratory tract, International Respiratory Forum. Reading UK: Colwood Publications; 1996. p. 19.
18. English AF, Neate MS, Quint DJ, Sareen M. Biological activities of some corticosteroids used in asthma. Am J Respir Crit Care Med 1994;149:A212.
19. Umland SP, Nahrebne MS, Razac S, Billah MM, Egan RW. Effects of mometasone furoate and other glucocorticoids on cytokine production from cultured peripheral blood CD4+ T cells. J Allergy Clin Immunol 1996;97:423.

20. Bickel CA, Stellato C, Schleimer RP. Comparison of the effect of inhaled glucocorticoids on human basophil histamine release and eosinophil viability. J Allergy Clin Immunol 1997;99:1632.
21. Kita H, Hagen JB, Gleich GJ. Fluticasone propionate is the most potent glucocorticoid in the induction of apoptosis of eosinophils. In: Acute and chronic inflammation in the respiratory tract, International Respiratory Forum. Reading UK: Colwood Publications; 1996. p. 17.
22. Johnson M. Anti-inflammatory properties of fluticasone propionate. Int Arch Allergy Immunol 1995;107:439-40.
23. Adler KB, Krunkosky TA, Fischer BM. Effects of tumour necrosis factor-alpha on airway epithelial cells in vitro. In: Acute and chronic inflammation in the respiratory tract, International Respiratory Forum. Reading UK: Colwood Publications; 1996. p. 18.
24. Abbinante-Nissen JM, Simpson LG, Leikauf GD. Corticosteroids increase secretory leukocyte protease inhibitor transcript levels in airway epithelial cells. Am J Respir Crit Care Med 1994;149:A869.
25. Dahlberg E, Thalén A, Brattsand R, Gustafsson JA, Johansson U, Römpke K. Correlation between chemical structure, receptor binding, and biological activity of some novel, highly active, 16α, 17α-acetyl-substituted glucocorticoids. Mol Pharmacol 1983;25: 70-8.
26. Booth H, Gardiner PV, Ward C, Walls A, Hendrick DJ, Walters EH. Effect of fluticasone on airway inflammation as assessed by bronchoalveolar lavage (BAL). Eur Respir J 1993;6(suppl 17): 584S.
27. Möller GM, Overbeek SE, van Helden-Meeuwsen CG, de Jong TAW, Mulder PG, Drexloge HA, et al. Glucocorticoid therapy is associated with modulation of dendritic cells in bronchial mucosa of atopic asthmatic subjects. In: Acute and chronic inflammation in the respiratory tract, International Respiratory Forum. Reading UK: Colwood Publications; 1996. p. 16.
28. Warner JA, Shute JK, Howarth PH. Effect of therapy on matrix metallo-proteinase (MMP) activity in the broncho-alveolar lavage (BAL) of patients with mild asthma. Am J Resp Crit Care Med In press.
29. Derendorf H, Hochhaus G, Möllermann H, Barth J, Krieg M, Jurn S, et al. Receptor-based pharmacokinetic-pharmacodynamic analysis of corticosteroids. J Clin Pharmacol 1993;33:115-23.

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	10518016
Filing Date	2005-07-06
First Named Inventor	Amar Lulla
Art Unit	1616
Examiner Name	Kristie Latrice Brooks
Attorney Docket Number	PAC/20632 US (4137-04700)

U.S.PATENTS Remove

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

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

U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20060110331	A1	2006-05-25	Dang, et al.	
	2	20070020330	A1	2007-01-25	Dang, et al.	
	3	20100152147	A1	2010-06-17	Fuge, et al.	

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

FOREIGN PATENT DOCUMENTS Remove

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	10518016
	Filing Date	2005-07-06
	First Named Inventor	Amar Lulla
	Art Unit	1616
	Examiner Name	Kristie Latrice Brooks
	Attorney Docket Number	PAC/20632 US (4137-04700)

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

NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	HODGES, NORMAN, et al., "Antimicrobial Preservative Efficacy Testing," Handbook of Microbiological Quality Control, Pharmaceuticals and Medical Devices, 2000, Page 168 plus cover page and publication page, Rosamund M. Baird, et al., Editor, Taylor & Francis Publisher, USA and Canada.	☐
	2	HERRERO, VANRELL, R., "Preservatives in Ophthalmic Formulations: An Overview," Arch. Soc. Esp. Oftalmol, 2007, Vol. 82., pgs. 531-532.	☐
	3	JOHNSON, MALCOM, "Development of fluticasone propionate and comparison with other inhaled corticosteroids," J. Allergy Clin. Immunol., April 1998, Vol. 101, No. 4, Part 2, pgs. S434-S439.	☐

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

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

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

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	10518016
	Filing Date	2005-07-06
	First Named Inventor	Amar Lulla
	Art Unit	1616
	Examiner Name	Kristie Latrice Brooks
	Attorney Docket Number	PAC/20632 US (4137-04700)

CERTIFICATION STATEMENT

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

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

OR

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

☐ See attached certification statement.

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

☐ None

SIGNATURE

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

Signature	/Rodney B. Carroll/	Date (YYYY-MM-DD)	2010-09-24
Name/Print	Rodney B. Carroll	Registration Number	39624

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

Privacy Act Statement

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

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

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

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

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

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

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

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

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

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

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Amar Lulla, *et al.*	§	
		§	Group Art Unit: 1616
Serial No.:	10/518,016	§	
		§	Examiner: Kristie Latrice Brooks
Filed:	July 6, 2005	§	
		§	Confirmation No.: 4912
For:	COMBINATION OF AZELASTINE AND STEROIDS	§	
		§	

DECLARATION UNDER 37 CFR § 1.132

I, Geena Malhotra, hereby declare and say that:

1. I am a co-inventor of the invention claimed in the above-identified patent application.

2. Attached as Exhibit A is comparison data for five compositions:

   Column 1: Azelastine.HCl
   Column 2: Budesonide
   Column 3: Azelastine.HCl & Budesonide
   Column 4: Fluticasone Propionate
   Column 5: Azelastine.HCl and Fluticasone Propionate

Table I of Exhibit A sets for the ingredient list for the five compositions. Table II of Exhibit A sets forth comparative stability data for the five compositions. The results in Table II show the impurity levels in the initial compositions, and after storage under certain conditions: for example "25/60 RH at 1 M" means the composition was stored for one month at a temperature of 25 degrees C and at a relative humidity of 60. The results in Table II show that the individual active materials (e.g., azelastine.HCl, budesonide, and fluticasone

propionate) have good stability, in that the impurity levels are fairly constant in all the tests. The results in Table II also show that the combination of azelastine and budesonide are relatively unstable, with varying, and high amounts of impurities developing during the tests. Surprisingly, the results for azelastine and fluticasone show good stability throughout the tests, as the amount of impurity remains constant and at a low level.

3. Attached as Exhibit B is a compilation of statements from 6 medical practitioners, labeled B1-B6, along with typed transcriptions. As is self-evident, these statements attest to various advantages and superior results associated with patient use of the DUONASE product comprising azelastine and fluticasone.

4. A pharmaceutical formulation comprising azelastine and fluticasonse is commercially available where approved as DUONASE nasal spray, as shown in attached Exhibit C containing information from the following website:
http://www.cipladoc.com/therapeutic/admin.php?mode=prod&action=disp&id=213.

5. Attached as Exhibit D are descriptions of the testing method used to generate the stability data discussed in Exhibit A. Exhibit D also states the nature of the impurities observed in the compositions described in Exhibit A and how those impurities were detected.

6. Based on my analysis of the entirety of data provided in the Exhibit A, I have concluded that the azelastine and fluticasone composition displays an unexpectedly beneficial stability when compared to the azelastine and budesonide composition.

7. I am unaware of another commercially available pharmaceutical formulation comprising an antihistamine and a steroid.

8. The present application is licensed to Meda Pharmaceuticals.

9. I, Geena Malhotra, further 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 are made with the knowledge that willful false statements and the like so made are punishable by fine, 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 this application or any patent issuing thereon.

Date: September 23, 2010

g.malhotra

Geena Malhotra

Comparative Composition data of Azelastine with steroids

Ingredients	**Azelastine (%w/~~w~~v)**	**Budesonide (%w/w)**	**Azelastine + Budesonide (%w/w)**	**Fluticasone (%w/w)**	**Azelastine + Fluticasone (%w/~~w~~v)**
Drugs	137 mcg	64 mcg	137 + 64 mcg	50 mcg	140 + 50 mcg
MCC+CMC (Avicel RC)	–	-	2.0	~~0.75~~1.5	~~2.0~~1.5
HPMC	0.10	-	-	-	-
Dispersible cellulose	-	1.25	-	-	-
Dextrose Anhy.	-	-	-	~~2.5~~5.0	-
Anhy. Glucose	-	5.0	-	-	-
Glycerin	-	-	2.3	-	~~2.3~~2.6
Polysorbate 80	-	0.016	0.005	0.~~0025~~005	0.~~005~~025
BKC ~~10% w/v solution~~ NF	0.0125	-	0.005	~~100 ml~~0.02	0.1~~0~~
Phenyl ethyl alcohol	-	-	-	0.~~1~~25	0.25
Pot sorbate	-	0.12	-	-	-
Disodium EDTA	0.05	0.01	0.01	-	~~0.01~~
Sodium Chloride	0.68	-	-	-	-
Citrate Monohydrate	0.048	-	-	-	-
Disodium Phosphate	0.322	-	-	-	-
Hydrochloric acid	-	q.s.	-	-	-

Comparative Stability data of Azelastine with steroid Compositions

Stability tests	Azelastine	Budesonide	Azelastine + Budesonide	Fluticasone	Azelastine + Fluticasone
	INITIAL	**INITIAL**	**INITIAL**	**INITIAL**	**INITIAL**
Assay	100	97.6	98+97	101.6	100+101.12
PH	6.78	4.51	6.0	6.4	6.1
Total Impurity	0.03	0.26	<0.1 +2.32 ~~+0.11~~	0.52	0.08+ 0.6
	25/60 RH at 1M	**25/60 RH at 1M**	**25/60 RH at 1M**	**25/60 RH at 1M**	**25/60 RH at 1M**
PH	6.86	4.68	5.94	Not Done	Not Done
Total Impurity	0.12	0.25	<0.1+ 0.97 ~~+0.07~~	Not Done	Not Done
	25/60 RH at 3 M	**25/60 RH at ~~3M~~ 2M**	**25/60 RH at 3 M**	**25/60 RH at 3 M**	**30/65 RH at ~~1M~~ 3M**
PH	6.76	4.6	5.96	6.21	5.85
Total Impurity	0.13	0.42	<0.1+5.39 ~~+0.16~~	0.46	0.2+0.84
	40/75 RH at 1M	**40/75 RH at 1M**	**40/75 RH at 1M**	**40/75 RH at 1M**	**40/75 RH at 1M**
PH	6.86	4.69	5.92	6.35	5.82
Total Impurity	0.13	0.29	<0.1+5.53 ~~+0.05~~	0.52	0.4+0.89
	40/75 RH at 3M	**40/75 RH at ~~3M~~ 2M**	**40/75 RH at 3M**	**40/75 RH at 3M**	**40/75 RH at 3M**
PH	6.76	4.61	5.91	5.98	5.81
Total Impurity	0.18	0.49	<0.1+18.29 ~~+0.23~~	0.53	0.37+0.85

Exhibit B1

Dr. C. M. Mathew Chooracken
B. Sc., M. B. B. S., M. S. (E. N. T.) D. L. O.
Senior Specialist in E.N.T.
Civil Surgeon
District Hospital, Kottayam
Reg. No. 9473

Consultation:
Behind Margin Free Market
Near Kottayam East Police Station
Collectorate P.O., Kottayam - 686 002
Ph: 2564864, Mb: 9447288822

To Cipla Respiratory L

I have been using the Deconase nasal spray regularly for my nasal allergy patients. I found it to be very effective when compared to the available other nasal sprays. Oral medication can be avoided as well.

Kottayam
23/8/05

Dr. C. M. Mathew Chooracken
B. Sc., M. B. B. S., M. S. (E. N. T.) D. L. O.
Senior Specialist in E. N. T.
Civil Surgeon,
District Hospital, Kottayam
Reg. No. 9473

Dr. C.M.MATHEW CHOORACKEN

To Cipla Respiratory

I have been using the Duonase nasal spray regularly for my nasal allergic patients. I found it is very effective when compared the available other nasal sprays. Oral medication can be avoided as well.

Kottayam
23/8/05

Exhibit B2

Confidential

डॉ. पी.एन. तेजनकर
एम. एस. (ई.एन.टी.)
नाक, कान, गला एवं गर्दन रोग विशेषज्ञ
पूर्व रजिस्ट्रार ई.एन.टी. हॉस्पिटल, बाम्बे

क्लिनिक

गुजराती समाज, नई सड़क, उज्जैन ☎ 2561981 समय प्रातः 11 से 2.00

जय मेडिकल सेन्टर (बसावड़ा पेट्रोल पम्प के पा घंटाघर, फ्रीगंज, उज्जैन ☎ 2514684 समय सायं 6 से 8.30

रविवार अवकाश

विशेषज्ञ

• नाक एवं सायनस इन्डोस्कोपी (दूरबीन द्वारा आपरेशन) • माइक्रोलेरिन्जियल सर्जरी
• माइक्रोईयर सर्जरी (जर्मनी, फ्रांस एवं स्वीटजरलैण्ड से प्रशिक्षण प्राप्त) • नाक की प्लास्टिक सर्जरी (राईनोप्लास्टी)

18.8.08

Regarding Duonase

Using this product for last so many days.

This is ideal, first line agent for the patient. The combination is adequate to deal with all types of allergy. It

- Acts on both phases (early and late phase of allergy i.e. inhibits)
- antagonise the H1 receptor activity & few side effects.
- Acts on multiple symptoms

The systemic bioavailability is less so can be used for a longer period without side effects.

Tough to allergy Safe to Users

[signature]

DR.P.N.TEJANKAR

M.S. (E.N.T)
E.N.T and Neck Specialist
Ex-Registrar E.N.T. Hospital, Bombay

CLINIC

Gujrati Samaj,
Nai Sadak, Ujjain
☎ 2561981
Time Mor: 11 to 2.00
SUNDAY

Jai Medical Centre (Near
Vasavda petrol pump)
Ghantaghar, Freegunj, Ujjain
☎ 2514884
Time:eve. 6 to 8.30
HOLIDAY

Specialist

• Nose and sinus endoscopy • Microlaryngeal Surgery • Microear Surgery (Trained from Germany, France and Switzerland) •Plastic Surgery of the Nose (rhinoplasty)

Regarding Duonase

Using this product for last so many days. This is ideal, first line agent for the patient. The combination is adequate to deal with all type of allergy.

- Acts on both phases (early as well as late phase of allergy i.e. inhibit)

- Antagonises the H1 receptor activity with few side effect.

- Acts on multiple symptoms.

- The systemic bioavailability is less so can be used for a longer period without side effect.

Tough to allergy safe to Nose

Confidential

डॉ. प्रसाद र. जवळेकर एम. एस. (ई. एन. टी.)

रजि. नं. ०७१८८२
कृष्णा जनरल हॉस्पिटल
गल्लाणे हेल्थ लॉन, पी. के. एम. टी. चौक, भोसरी,
पुणे ४११०३९. फोन २७५२९५१६
वेळ : संध्या. ५ ते ८-०० वा.

रविवार बंद

(क्लिनिक-ओ-क्लासा
धन्वंतरी फार्म, नाक, घसा हॉस्पि
ओक्स रोड, नायगाव
ता. हवेली, जि. पुणे, ४१०
फोन (हॉस्पि.) २४४७६६, (नि.) २४३

Date. 27.8.05

I have prescribed "Duonase Nasal Spra for 258 patients since Aug 2004 to Aug 2005. And I found that Duonase Nasal Spray very very effective in all types of allergi rhinitis. Especially in "seasonal allerg rhinitis." Fluticasone alone or azelast alone also has been tried. But sing drug was not effective as compared with the combination of both i.e "Duonase Nasal Spray."

So I hereby strongly recommen Duonase Nasal Spray for allergic rhi

DR. PRASAD JAWALEKAR M.S (E.N.T)

Reg.no.071882
Krishna General Hospital
Gavhane building, P.C.M.T Chowk,
Bhosari,Pune 411039. ☎ 27129516
Time: eve. 5-00 to 8-00 SUNDAY CLOSED

E.N.T Specialist
Dhanvantari E.N.T.Hospital
Khodad Road, Narayangaon,
Taluka Junnar, Dist. Pune 410504
☎02132-(Hosp.)244766 (R)243969

I have prescribed "Duonase Nasal spray" for 258 patients since Aug 2004 to Aug 2005. And I found that Duonase Nasal Spray very very effective in all types of allergic rhinitis. Especially in "Seasonal allergic rhinitis", Fluticasone alone or azelastine alone also has been tried. But single drug was not effective as compared with the combination of both i.e. "Duonase Nasal Spray".

So I hereby strongly recommend Duonase Nasal Spray for allergic rhinitis.

Exhibit B4

Confidential

No: 25469

Dr. Manish Munjal

M.B.B.S., M.S. Diplomate of National Board (ENT), M.N.A.M.S.
D.H.A., D.N.D., D.N.A., D.T.M., DM.S.
EAR – NOSE – THROAT AND HEAD-NECK SURGEON

Ph.: 2300182
Mobile : 98551-23462
E-mail : mmunjal@glide.net.in

Consultant Otorhinolaryngology & Head-Neck Services
Dayanand Medical College & Hospital, Ludhiana
Formerly Consultant Christian Medical College
and Brown Hospital, Ludhiana.

Clinic-cum-Residence
52-C, Udham Singh Nagar,
Adj. P.A.U. Gate No.4,
Next to Lions Bhawan, Ludhiana

To

Sp.

Av.

Pr.

Pro

Le

I have been using nasal sprays from the year 1993, ever since I joined my present institution. I have used beclomethasone, budesonide, azelastine, fluticasone, mometasone, with oral antihistaminics. Long Term Treatment of: down the line till date.

Rin.

The present combination spray of a weak (non-decongestant component) azelastine and fluticasone (steroidal component) is comparable by itself in my patients of chronic simple rhinitis, following nasal polyposis surgery and nose correction surgery or septal surgery. Cross Consult: 5mm

Web.

There is a response noted within a week in a few patients but the maximum

Opp.

Sd.

Consultations : Evening 2.30 P.M. to 3.30 P.M. 5.30 P.M. to 7.30 P.M.
Morning by appointment only Sunday : 10.30 to 1.00 P.M.

Number of patients responded very well after three weeks of therapy.

Recurrences of polyposis after functional endoscopic sinus surgery is markedly reduced. Eye itching, crusting and nasal bleeding as noted with earlier preparations is not noted to that much extent

Of course caution/avoidance in diabetic and hypertensive patients is required for fear of worsening & inducing a fungal pathology (though have not found much literature on this issue on the net)

The combination therapy (Dexycom) is gradually tapered off by me in two to three months time.

Occasionally usage is not advised the entire bottle must be finished for having the best of results.

Hoping the future is bright for this combination and no one digs up some controversy/criticism of it like they

DR. MANISH MUNJAL

I have been using nasal sprays from the year 1993, ever since I joined my present institution. I have used Beclomethasone, Budesonide, Azelastine, Fluticasone, Mometasone, with oral antihistamines down the line till date.

The present combination spray of a weak (non sedating component) Azelastine and fluticasone (steroid component) is complete by itself in my patients of chronic simple rhinitis following nasal + sinus polyposis surgery and those unwilling for surgery or unfit for surgery.

There is a response noted within a week in a few patients but the maximum number of patients respond very well after three weeks of therapy.

Recurrences of polyposis after functional endoscopic sinus surgery is markedly reduced. Eye itching, crusting and nasal bleed as noted with earlier preparations is not noted to that much extent of course caution/avoidance in diabetic and hypertensive patients is required for fear of worsening or inducing and fungal pathology (though have not found much literature on the issue on the net).

The combination Therapy (DUONASE) is gradually tapered off by me in two to three months time.

Occasionally usage is not advised. The entire bottle must be finished for having the best of results.

Hoping the future is bright for this combination and no one digs up some contra indication or side effect of this indication.

Exhibit B5

VATS E.N.T. CENTRE

(दिल्ली सरकार द्वारा पंजीकृत)

690/5, Yamuna Vihar Road, (Road No. 68), Maujpur, Delhi-110053

: 229111
Ph. : 22916
: 22911

Dr. Suresh Vats

M.B.B.S., M.S. (ENT)
CONSULTANT EAR, NOSE & THROAT SURGEON
Formerly ENT Surgeon
ST. STEPHEN'S HOSPITAL
LNJP & GB PANT HOSPITAL

डॉ० सुरेश वत्स

एम.बी.बी.एस., एम.एस.(ई.एन.टी.)
कान, नाक व गला रोग विशेषज्ञ एवं सर्जन
समय : सुबह 10 से 1 बजे शाम 6 से 9 बजे
Rehabilitation Yes/No. S. No. ..... (रविवार अवकाश)

Name ..... Age & Sex ..... Resl. ..... Date ..... Ad

परिक्षण हेतु केवल: Audiometory एवं Speech Therapy
सोम, बुध, शुक्र सुबह 10 से 1 व संगल शाम 7 से 8 बजे
P.T. Audiogram/Hearing Assessment
Aided Audiogram
Hearing Aid Trial
Speech Assessment
Speech Therapy
Calorie Test
Impedance

Hb TLC, DLC, B.T., C.T.
ESR, Mx-Test
Blood Sugar R.B.Rs, Blood Urea
Urine R/E & M/e
Prothrombin Time Platelets Count
HBsAg, HIV 1 & II
AEC IgE, Nasal smear for Eosinophils
VDRL, ASLO Titre
T3 T4 TSH
Sputum/Urine for AFB
Throat/Nasal/Ear/Swab C & S
Blood - aval & cyst
FNAC

X-Ray Mandible - Lat. Obliques(Rt) Towns
X-Ray PNS - Waters
X-Ray Naso-Pharynx-soft Tissue (Lateral)
X-Ray Neck soft Tissue - Lateral
X-Ray cervical Spine - Lat. & A/P
X-Ray - Styloid Palpoces (Rt Lateral)
X-Ray Occlusal view for of mouth
X-Ray - Submandibular region - Lat. Pt. - Lt
X-Ray - Internal Auditory Meatus
X-Ray T.M. Joint Lat. Open & closed Jaw
X-Ray - Nasal Bones - Lateral
X-Ray Skull - AP - Lateral
X-Ray - Chest P.A. View
Barium Swallow
C.T. Scan - PNS - Coronal 3 mm cuts
C.T. Scan - Temporal bones
C.T. Scan - Neck - Nasal
E.C.G.

R L

Rinne's
Weber's

I/L Exa.:

Right Left

Duonase nasal spray is a unique distinct from available nasal spray due to it's combined anti allergic & anti myocardial property. It is an oral product, effective in the treatment of Allergic Rhinitis with or without concomitant bronchial

Allergy: Worth Trying to Say
to use in certain patients if
oral antihistamine may be harmful

17/8/05

Dr. SURESH VATS
M.S. (ENT)
Sr. CONSULTANT EAR, NOSE &
THROAT SURGEON
Reg. No. MCI-2106, DMC-2712
69B/5, Road No 06, Manjpur, Delhi-53

Dr. SURESH VATS

Duonase Nasal spray is unique & distinct from other available nasal sprays due to it combined Anti-allergic & anti-inflammatory properties. It is an excellent product, effective in majority of patients with allergic Rhinitis with or without concomitant Bronchial Allergy. Worth Trying. Safe to use in certain patients where oral antihistamine may be harmful.

Exhibit B6

डॉ. बी. बी. माथुर
एम.डी.

वरिष्ठ विशेषज्ञ एवं एसोसियट प्रोफेसर
चेस्ट एवं टी.बी. विभाग
सरदार पटेल मेडिकल कॉलेज, बीकानेर
RMC No. 7468

Dr. B. B. Mathur
M.D.

Senior Consultant & Associate Professor
Chest & T.B., Hospital
S.P. Medical College, BIKANER
✆ Hos. :0151-2226333, Res. 0151-2528789

Ref No.

Date 17/8/05

1) Nasonex Nasal Spray is highly effective in controlling symptoms and subsequent relapse in patients of Allergic Rhinitis. I have used this product in many patients and due to its efficacy it gives confidence to patients & it take care symptoms due to rapid onset of action and long lasting relief due to anti-inflammatory activity

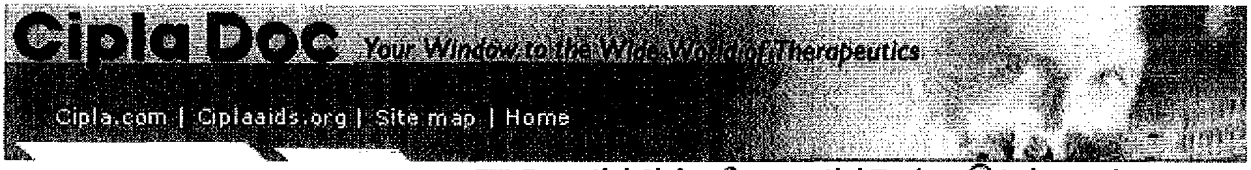
डॉ. बी. बी. माथुर
एसोसियट प्रोफेसर
चे. टी. एंड टी.बी. विभाग
सरदार पटेल मेडिकल कॉलेज
बीकानेर (राज.)

निवास—III/7, मेडिकल कॉलेज कैम्पस, नागनेचीजी रोड, बीकानेर 334003 ✆ 0151-2528789
Resi. : III/7, Medical College Campus, Nagnechiji Road, Opposite Swimming Pool, BIKANER ✆ 0151-2528789

Dr. B.B. MATHUR

Duonase Nasal spray is highly effective in controlling symptoms and subsequent relapse in patients of Allergic Rhinitis. I have used this product in many patients and due to its efficacy it gives confidence to patients as it take care symptoms due to rapid onset of action and long lasting relief due to anti-inflamattory action.

Exhibit C



Cipla

Therapeutic Index

Nasal Preparations

Duonase Nasal Spray

Azelastine hydrochloride & Fluticasone propionate

Each spray delivers
Azelastine hydrochloride BP ..... 140 mcg
Fluticasone propionate BP ..... 50 mcg

Composition
Fluticasone propionate BP ..... 0.0357% w/v
Azelastine Hydrochloride BP ..... 0.10% w/v
Benzalkonium Chloride NF ..... 0.01% w/v
(as preservative)
Phenyl Ethyl alcohol USP ..... 025% v/v
(as preservative)

Description
Duonase is an antihistamine-corticosteroid combination available as a metered spray formulation for intranasal administration. It contains azelastine hydrochloride, which is a s generation H 1 receptor antagonist with potent topical activity and fluticasone propionate, synthetic corticosteroid with anti-inflammatory properties.

Pharmacology
As Duonase is a combination of Azelastine and Fluticasone; the pharmacological properti both the molecules are given separately.

Pharmacology of Azelastine Hydrochloride
Azelastine hydrochloride, a phthalazinone derivative, exhibits histamine H 1 -receptor ant activity in isolated tissues, animal models, and humans. The major metabolite, desmethylazelastine, also possesses H 1 -receptor antagonist activity.

Pharmacokinetics and Metabolism
After intranasal administration, the systemic bioavailability of azelastine hydrochloride is approximately 40%. Maximum plasma concentrations (Cmax) are achieved in 2-3 hours. I on intravenous and oral administration, the elimination half-life, steady-state volume of distribution, and plasma clearance are 22 hours, 14.5 L/kg, and 0.5 L/h/kg, respectively. Approximately 75% of an oral dose of radiolabeled azelastine hydrochloride was excreted feces with less than 10% as unchanged azelastine. Azelastine is oxidatively metabolized principal active metabolite, desmethylazelastine, by the cytochrome P450 enzyme system specific P450 isoforms responsible for the biotransformation of azelastine have not been identified; however, clinical interaction studies with the known CYP3A4 inhibitor erythromy failed to demonstrate a pharmacokinetic interaction. In a multiple-dose, steady-state drug interaction study in normal volunteers, cimetidine (400 mg twice daily), a nonspecific P45(inhibitor, raised orally administered mean azelastine (4 mg twice daily) concentrations by approximately 65%.

The major active metabolite, desmethylazelastine, was not measurable (below assay limit single-dose intranasal administration of azelastine hydrochloride. After intranasal dosing c azelastine hydrochloride to steady-state, plasma concentrations of desmethylazelastine r

from 20-50% of azelastine concentrations. When azelastine hydrochloride is administerec desmethylazelastine has an elimination half-life of 54 hours. Limited data indicate that the metabolite profile is similar when azelastine hydrochloride is administered via the intranas oral route.

Pharmacology of Fluticasone Propionate
Fluticasone propionate is a synthetic, trifluorinated corticosteroid with anti-inflammatory ac

In preclinical studies, fluticasone propionate revealed progesterone-like activity similar to natural hormone. However, the clinical significance of these findings in relation to the low levels is not known.

The precise mechanism through which fluticasone propionate affects allergic rhinitis symp not known. Corticosteroids have been shown to have a wide range of effects on multiple c types (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and me (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in inflammation.

Pharmacokinetics:
Absorption: Fluticasone propionate delivered by the intranasal route has an absolute bioavailability averaging less than 2%. After intranasal treatment of patients with allergic r for 3 weeks, fluticasone propionate plasma concentrations were above the level of detecti pg/mL) only when recommended doses were exceeded and then only in occasional samp low plasma levels. Due to the low bioavailability by the intranasal route, the majority of the pharmacokinetic data was obtained via other routes of administration. Studies using oral c of radiolabeled drug have demonstrated that fluticasone propionate is highly extracted fro plasma and absorption is low. Oral bioavailability is negligible, and the majority of the circ radioactivity is due to an inactive metabolite.

Distribution: Following intravenous administration, the initial disposition phase for flut propionate was rapid and consistent with its high lipid solubility and tissue binding. The vc distribution averaged 4.2 L/kg.

The percentage of fluticasone propionate bound to human plasma proteins averaged 91% obvious concentration relationship. Fluticasone propionate is weakly and reversibly bounc erythrocytes and freely equilibrates between erythrocytes and plasma. Fluticasone propio not significantly bound to human transcortin.

Metabolism: The total blood clearance of fluticasone propionate is high (average, 1,0 mL/min), with renal clearance accounting for less than 0.02% of the total. The only circula metabolite detected in man is the 17(beta)-carboxylic acid derivative of fluticasone propio which is formed through the cytochrome P450 3A4 pathway. This inactive metabolite had affinity (approximately 1/2,000) than the parent drug for the glucocorticoid receptor of hun cytosol in vitro and negligible pharmacological activity in animal studies. Other metabolite detected in vitro using cultured human hepatoma cells have not been detected in man.

Elimination: Following intravenous dosing, fluticasone propionate showed polyexpor kinetics and had a terminal elimination half-life of approximately 7.8 hours. Less than 5% radiolabeled oral dose was excreted in the urine as metabolites, with the remainder excre the feces as parent drug and metabolites.

Indications
Duonase is indicated for the management of symptoms of allergic rhinitis once the neec antihistamine and corticosteroid has been established. It is recommended to treat **mode severe persistent symptoms** in adults above 12 years. For children above 5 years **Duonase** is recommended for **severe symptoms** of allergic rhinitis. **Duonase** can used for treating non-allergic vasomotor rhinitis in adults and children 12 years of age anc

Dosage And Method of Administration
Adults and children 5 years and older: 1 spray/nostril twice daily

The recommended dosage should not be exceeded. Not recommended for use in childrer 5 years.

Contact Us

Essential Update

News Update
HIV/AIDS Update
Respiratory Update
Cardiology Update
Infection Update
Neurology Update
Ophthalmology Update
Disease of the month
Medical Slides
Conferences

Therapeutic Index

Cipla
Cipla Omnicare

New Introductions

Internationally
Cipla
Protec

Essential Reading

Publications
Patient help
Treatment guidelines

Search:

Go

www
www.cipladoc.com

Contraindications

Duonase is contraindicated in patients with or known hypersensitivity to azelastine hydroc or fluticasone propionate or any of the components of the preparation.

Warnings and Precautions

- Concurrent use of this combination with alcohol or other CNS depressants or othe antihistamines should be avoided as additional reductions in alertness and additio impairment of CNS performance may occur due to azelastine.
- The replacement of a systemic corticosteroid with a topical corticosteroid can be accompanied by signs of adrenal insufficiency. Some patients may experience syr of withdrawal e.g. joint and/or muscular pain, lassitude and depression.
- The concomitant use of an intranasal corticosteroid with other corticosteroids coul increase the risk of signs or symptoms of hypercorticism and/ or suppression of th axis. Therefore the combination should be used cautiously in patients with other pathological conditions requiring steroids.
- Intranasal corticosteroids may cause a reduction in growth velocity when administ higher dose. The recommended dosage of **Duonase** should not be exceeded.
- Special care is needed in patients with lung tuberculosis and fungal and viral infec Children who are on immunosuppressant drugs are more susceptible to infections healthy children. Chicken pox and measles for example can have a more serious a fatal course in children on immunosuppressant corticosteroids.
- During long term therapy, monitoring of hematological and adrenal function is adv
- In clinical studies with intranasal fluticasone propionate, the development of localiz infections of the nose and the pharynx with *Candida albicans* has been seen rarel such an infection develops, it may require treatment with appropriate local therapy discontinuation of the treatment with **Duonase** is advised

Drug Interactions

The use of **Duonase** in patients taking concurrent drugs, which are potent inhibitors of tl cytochrome 450 3A4 system eg. Ketoconazole and protease inhibitors such as ritonavir m associated with increased systemic exposure of fluticasone.

Pregnancy

The combination should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation

It is not known whether azelastine hydrochloride or fluticasone propionate is excreted in h milk. Hence, caution should be exercised while prescribing this combination to nursing mc

Undesirable Effects

The most likely side effects with this combination are headache, somnolence, pharyngitis, epistaxis, nasal burning/irritation, nausea, vomiting, cough, taste disturbance. The combir may produce a bitter taste, which may lead to occasional nausea. Bitter taste disappears sometime.

Shelf Life

2 years

Storage and Handling Instructions

Store below 30 ^{0} C.
Do not refrigerate.
Protect from direct sunlight.

Packaging Information

Duonase Nasal Spray
Sales pack contains 70 metered doses

Last Updated: M

News Updates | Cardiology Update | Infection Update | Treatment Guidelines
Respiratory Update | Neurology Update | Ophthalmology Update | Medline |
Medical Slides | Patient Help | Conferences | Forum | Medical Quiz | New Introdu
Disease of the Month | Interesting Links | New Introductions Internationally | Car
Therapeutic Index | Cipla.com | Contact

Sr. No	TEST		FLUTICASONE PROPIONATE AQUEOUS NASAL SPRAY
1	ASSAY	Preparation of Mobile Phase	Acetonitrile, Ammonium phosphate buffer pH 3.5 and methanol in the ratio of 15:35:50.
		Column	A stainless steel column 15 cm X 4.6 mm internal diameter packed with octadecylsilyl silica gel for chromatography (5 µm)
		Flow rate	About 1.5 ml/min
		Detection wavelength	239nm
		Column oven temperature	40°C
		Retention time	About 6.5minutes
		Run time	10 minutes
		Injection volume	100µl of each solution
		Diluent	Mobile Phase
		Standard preparation	1ppm Fluticasone propionate
		Sample preparation	1ppm Fluticasone propionate
2	RELATED SUBSTANCES	Preparation of Mobile Phase A	Acetonitrile and methanol (97: 3)
		Preparation of Mobile Phase B	Water, methanol and Orthophosphoric acid (97: 3: 0.1)
		Column	15 cm X 4.6mm column that contains 5µ packing L1 with guard column 50mm X 4.6mm, 5µ packing L1
		Flow rate	1.5 ml/min
		Detection wavelength	239nm
		Column oven temperature	40°C
		Run time	70 minutes
		Injection volume	100µl
		Diluent	Distilled Water: Acetonitrile (50:50)
		Standard preparation	100ppm Fluticasone propionate
		Reference preparation	1ppm Fluticasone propionate
		Sample preparation	100ppm Fluticasone propionate
		Impurities monitored	Fluticasone acid propionate
			Fluticasone acetate
			S-methyl Fluticasone
			Chloro Fluticasone
			Iodo Fluticasone

Sr. No	TEST		AZELASTINE HYDROCHLORIDE NASAL SPRAY
1	ASSAY	Preparation of Mobile Phase	Methanol, Ammonium phosphate Buffer and Acetonitrile in the ratio of (450:400:150), 1ml of Triethylamine, pH = 5.0
		Column	Octadecylsilyl C18, 25 cm X 4.6mm, 5µm column
		Flow rate	About 1.2 ml/min
		Detection wavelength	290nm
		Column oven temperature	25°C
		Retention time	About 6.0 minutes
		Run time	10.0 minutes
		Injection volume	20µl
		Diluent	Buffer : Acetonitrile: Methanol (350:350:300)
		Standard preparation	50ppm Azelastine HCl
		Sample preparation	50ppm Azelastine HCl
2	RELATED SUBSTANCES	Preparation of Mobile Phase A	Ammonium phosphate buffer, Acetonitrile, Methanol in the ratio of (510:140:350); adjust pH to 5.0 with 1ml of triethylamine
		Preparation of Mobile Phase B	Ammonium phosphate buffer, Acetonitrile, Methanol in the ratio of (300:300:400); adjust pH to 5.0 with 1ml of triethylamine
		Column	15 cm X 4.6mm column that contains 5µ packing L1 with 20mm X 4.0mm, guard of packing L1.
		Flow rate	1.0ml/min
		Detection wavelength	290nm
		Column oven temperature	40°C
		Run time	60 minutes
		Injection volume	50µl of each solution
		Diluent	Buffer : Acetonitrile: Methanol (350:350:300)
		Standard preparation	250ppm Azelastine HCl
		Reference preparation	2.5ppm Azelastine HCl
		Sample preparation	250ppm Azelastine HCl
		Impurities monitored	N-oxide A
			N-oxide B
			Impurity D

Sr. No	TEST		AZELASTINE HYDROCHLORIDE AND FLUTICASONE PROPIONATE NASAL SPRAY	
1	ASSAY	Preparation of Buffer solution	0.01M Ammonium dihydrogen orthophosphate, pH 3.5 with dilute orthophosphoric acid	
		Preparation of Mobile Phase	Methanol : Buffer solution : Acetonitrile (500 : 350 : 150)	
		Column	C8, 25 cm x 4.6mm, 5µm	
		Flow rate	1.5 ml/min	
		Detection wavelength	239 nm	
		Column oven temperature	40°C	
		Injection volume	20µl	
		Standard preparation	For Azelastine hydrochloride: about 50 ppm For Fluticasone propionate: about 18 ppm	
		Sample preparation	For Azelastine hydrochloride: about 50 ppm For Fluticasone propionate: about 18 ppm	
2	RELATED SUBSTANCES		Azelastine HCl	Fluticasone Propionate
		Preparation of Mobile Phase A	0.01M Ammonium dihydrogen phosphate, pH 3.5 with orthophosphoric acid	Acetonitrile, Methanol and orthophosphoric acid (970 :30:0.5)
		Preparation of Mobile Phase B	Acetonitrile and Methanol (1:1)	Water, Methanol and orthophosphoric acid (970 :30:0.5)
		Column	C18, 25cm x 4.6mm, 5µm	C18, 25cm x 4.6mm, 5µm
		Flow rate	1.0ml/min	1.0ml/min
		Detection wavelength	239nm	239nm
		Column oven temperature	40°C	40°C
		Injection volume	10µl of each solution	20µl of each solution
		Diluent	Methanol	Mobile phase A
		Standard preparation	About 500 ppm Azelastine HCl	About 175 ppm Fluticasone Propionate
		Reference preparation	About 1 ppm Azelastine HCl	About 0.175 ppm Fluticasone Propionate
		Sample preparation	About 500 ppm Azelastine HCl	About 178.5 ppm Fluticasone Propionate
		Impurities monitored	1-methyl-4-2-(benzolyhydrazino) azepan	Impurity A - 6α,9-difluoro-11β-hydroxy-16α-methyl-3-oxo-17-(propanoyloxy) androsta-1,4-diene-17β-carboxylic acid
				Impurity B - [[6α,9-difluoro-11β-hydroxy-16α-

	yl]carbonyl]sulphenic acid
	Impurity C - 6α,9-difluoro-17-[[(fluoromethyl) sulphanyl]carbonyl]-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-dien-17α-yl acetate
	Impurity D - 6α,9-difluoro-17-[(methylsulphanyl)carbonyl]-11β-hydroxy-16α-methyl-3-oxo androsta-1,4-dien-17α-yl propanoate
	Impurity E - 6α,9-difluoro-17-[[(fluoromethyl)sulphanyl]carbonyl] -11β-hydroxy-16α-methyl-3-oxoandrost-4-en-17α-yl propanoate
	Impurity F - 6α,9-difluoro-17-[[(fluoromethyl)sulphanyl]carbonyl] -16α-methyl-3,11-dioxoandrosta-1,4-dien-17α-yl propanoate
	Impurity G - 6α,9-difluoro-17-[[(fluoromethyl)sulphanyl]carbonyl] -11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-dien-17α-yl 6α,9-difluoro-11β,17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carboxylate
	Impurity H - 17,17′-(disulphanediyldicarbonyl) bis(6α,9-difluoro-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-dien-17α-yl) dipropanoate
	Impurity I - 7,17′-(trisulphanediyl dicarbonyl)bis(6α,9-difluoro-11β-hydroxy-16α-methyl-3-oxo androsta-1,4-dien-17α-yl) dipropanoate

Sr. No	TEST		BUDESONIDE NASAL SPRAY
1	ASSAY	Preparation of Mobile Phase	Acetonitrile : Distilled water (65 : 35)
		Column	C18, 25 cm x 4.6mm, 5µm
		Flow rate	2.0 ml/min
		Detection wavelength	242 nm
		Column oven temperature	25°C
		Run time	5 minutes
		Injection volume	20µl
		Diluent	Mobile phase
		Standard preparation	20 ppm
		Sample preparation	20 ppm
2	RELATED SUBSTANCES	Preparation of Mobile Phase	0.025M Sodium phosphate Buffer pH 3.2 and Acetonitrile in the ratio of (720 :280)
		Column	Octadecylsilicagel C18, 25cm x 4.6, 5µm
		Flow rate	1.5ml/min
		Detection wavelength	240nm
		Column oven temperature	25°C
		Run time	60 minutes
		Injection volume	20µl of each solution
		Diluent	Acetonitrile and mobile phase
		Standard preparation	320ppm
		Reference preparation	3.2ppm
		Sample preparation	320ppm
		Impurities monitored	Desonide (Imp F as per Ph Eur)
			21 - Dehydrobudesonide epimer I (Imp D as per USP)
			21 - Dehydrobudesonide epimer II (Imp D as per USP)

Sr. No	TEST		AZELASTINE + BUDESONIDE NASAL SPRAY	
1	ASSAY	Prepration of Mobile Phase B	0.01M Ammonium phosphate Buffer,Acetonitrile and methanol (300:300: 400)	
		Column:	C18, 25 cm x 4.6mm column that contains 5µ packing	
		Flow rate:	1.0 ml/min	
		Detection wavelength:	242nm	
		Column oven temperature:	45°C	
		Run time:	9 minutes	
		Injection volume:	20µl	
		Diluent	Buffer,Acetonitrile and methanol (350:350: 300)	
		Standard preparation	20ppm Azelastine	10ppm Budesonide
		Sample preparation	20ppm Azelastine	9.3ppm Budesonide
2	RELATED SUBSTANCES	Prepration of Mobile Phase A	Buffer,Acetonitrile and methanol (51:14: 35)+1 ml of TEA /litre----- pH 5.0 with Orthophosphoric acid	
		Prepration of Mobile Phase B	Buffer,Acetonitrile and methanol (30:30: 40)+1 ml of TEA /litre----- pH 5.0 with Orthophosphoric acid	
		Buffer	1.15 gm Ammonium dihydrogen ortho phosphate-------->1000 ml Distilled water	
		Column:	C18, 15 cm X 4.6mm column that contains 5µ packing with C18 guard column	
		Flow rate:	1.0 ml/min	
		Detection wavelength:	254nm	
		Column oven temperature:	40°C	
		Run time:	70 minutes	
		Injection volume:	50µl	
		Diluent	Buffer,Acetonitrile and methanol (35:35: 30)	
		Standard preparation	250ppm Azelastine	100ppm Budesonide
		Reference preparation	2.5ppm Azelastine	1ppm Budesonide
		Sample preparation	250ppm Azelastine	117ppm Budesonide
		Impurities monitored	N-oxide A impurity of Azelastine	
			N-oxide B impurity of Azelastine	
			Impurity D of Azelastine	
			Impurity D of Budesonide (as per Ph Eur.)	
			Impurity A of Budesonide (as per Ph Eur.)	
			Impurity B of Budesonide (as per Ph Eur.)	
			Impurity F of Budesonide (as per Ph Eur.)	
			Impurity E of Budesonide (as per Ph Eur.)	
			Impurity G of Budesonide (as per Ph Eur.)	

Electronic Patent Application Fee Transmittal

Application Number:	10518016
Filing Date:	06-Jul-2005
Title of Invention:	Combination of azelastine and steroids
First Named Inventor/Applicant Name:	Amar Lulla
Filer:	Rodney B. Carroll/Linda Kerrick
Attorney Docket Number:	PAC/20632 US (4137-04700)

Filed as Large Entity

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

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 2 months with $0 paid	000607 1252	1	490	490

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**670**

Electronic Acknowledgement Receipt

EFS ID:	8487591
Application Number:	10518016
International Application Number:	
Confirmation Number:	4912
Title of Invention:	Combination of azelastine and steroids
First Named Inventor/Applicant Name:	Amar Lulla
Customer Number:	30652
Filer:	Rodney B. Carroll/Linda Kerrick
Filer Authorized By:	Rodney B. Carroll
Attorney Docket Number:	PAC/20632 US (4137-04700)
Receipt Date:	24-SEP-2010
Filing Date:	06-JUL-2005
Time Stamp:	19:02:59
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$670
RAM confirmation Number	5530
Deposit Account	501515
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
00001					

1		092410_ResponsetoFinalOA.pdf	855207 f63a077204847ca05cdb4dd57a061f62b8ab2cdb	yes	32

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Amendment After Final	1	1
Claims	2	8
Applicant Arguments/Remarks Made in an Amendment	9	32

Warnings:					
Information:					
2	Information Disclosure Statement (IDS) Filed (SB/08)	092410_IDS.pdf	817083 4497d3c13482a22a6607f47de3f883e4e54a7238	no	4
Warnings:					
Information:					
3	NPL Documents	HODGES_Antimicrobial.pdf	124468 30c5de52dc3c7936381c2e5297ab97ff71c7c9e3	no	3
Warnings:					
Information:					
4	NPL Documents	HERRERO_Preservatives.pdf	38317 a87e016c663fa6e655083d6d02aa9bb483ed2358	no	2
Warnings:					
Information:					
5	NPL Documents	JOHNSON_Development.pdf	176277 1366a2c655967b4710273ce704739c994fc3b425	no	6
Warnings:					
Information:					
6	Rule 130, 131 or 132 Affidavits	ExecutedInventorDeclarationWithAllExhibits.pdf	800299 343f6401a21980dfb6325689b02ace75c60d0e97	no	29
Warnings:					
Information:					
7	Fee Worksheet (PTO-875)	fee-info.pdf	32303 261eee0e700d08885584aab86a3325b3f5a6ec6e	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	2843954		

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 10/518,016	Filing Date 07/06/2005	☐ To be Mailed

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☐		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☒ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	**300**
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	**300**

APPLICATION AS AMENDED – PART II

AMENDMENT		(Column 1)		(Column 2)	(Column 3)	SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
	09/24/2010	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 33	Minus	** 51	= 0	X $ =		OR	X $52=	0
	Independent (37 CFR 1.16(h))	* 4	Minus	***6	= 0	X $ =		OR	X $220=	0
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	**0**

AMENDMENT		(Column 1)		(Column 2)	(Column 3)					
		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/GLORIA TRAMMELL/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/518,016	07/06/2005	Amar Lulla	PAC/20632 US (4137-04700)	4912

30652 7590 04/28/2010

CONLEY ROSE, P.C.
5601 GRANITE PARKWAY, SUITE 750
PLANO, TX 75024

EXAMINER	
BROOKS, KRISTIE LATRICE	
ART UNIT	**PAPER NUMBER**
1616	
MAIL DATE	**DELIVERY MODE**
04/28/2010	PAPER

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

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

Office Action Summary	Application No.	Applicant(s)	
	10/518,016	LULLA ET AL.	
	Examiner	Art Unit	
	KRISTIE L. BROOKS	1616	

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

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 July 2009*.

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) *1,2,4,6-22,25-30,35-38,44,45 and 53-56* is/are pending in the application.

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

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,6-22,25-30,35-38,44,45 and 53-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

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

Application Papers

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

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

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

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/23/09;8/7/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

1. Claims 1, 2, 4, 6-22, 25-30, 35-38, 44-45 and 53-56 are pending. Claims 53-56 are new.

2. Receipt and consideration of Applicants remarks/arguments submitted on July 23, 2009 is acknowledged.

3. Rejections not reiterated from the previous Office Action are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set of rejections presently being applied to the instant application.

Claim Rejections - 35 USC § 103

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

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

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

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5. Claims 1-2, 4, 7-21, 30, 35-38, 44-45, and 53-56 are rejected under U.S.C. 103(a) as being unpatentable over Cramer (EP 0780127).

Applicant claims a pharmaceutical formulation which comprises azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof and fluticasone, or a pharmaceutically acceptable ester thereof, wherein fluticasone or a pharmaceutically acceptable ester thereof in an amount from about 50micrograms/ml to about 5mg/ml of the formulation.

Determination of the scope and content of the prior art (MPEP 2141.01)

Cramer teaches a nasal spray composition comprising about 0.001 to about 0.2% concentration of a glucocorticosteroid (i.e. beclomethasone, flunisolide, triamcinolone, fluticasone, mometasone, bedusonide and pharmaceutically acceptable salts), 0.01 to about 4% concentration of an antihistamine (i.e. azelastine or pharmaceutically acceptable salt thereof, and an intranasal carrier (see the abstract and page 2 lines 36-45). The composition may contain isotonic agents such as citric acid, boric acid, propylene glycol, etc., thickening agents such as xanthan gum, microcrystalline cellulose, carboxymethyl cellulose, hydroxypropyl cellulose, etc., humectants such as sorbitol, propylene glycol, polyethylene glycol, etc. and preservatives such as

benzyl alcohol, phenylethyl alcohol, and quaternary ammoniums such as benzalkonium chloride (see page 4 lines 50-58 and page 5 lines 1-22). The composition may contain surfactants such as Polysorbate 80, Octoxynol, etc. (see page 5 lines 11-16). The pH of the composition is from about 4.5 to about 9 (see page 2 lines 57-58). The composition may be formulated into a nasal solution (for use as drops or a spray), a nasal suspension, ointment, or gel (see page 3 lines 43-47). Typically the dosage units may be prepared to deliver 0.5mcg to about 100mcg of the glucocorticoid and 5mcg to about 1000mcg of the antihistamine spray (see page 3 lines 58 and page 4 lines 1-2).

Example III discloses an intranasal pharmaceutical composition prepared by combining the following components utilizing conventional mixing techniques, shown below:

Component	Wgt %
triamcinolone acetonide	0.050
azelastine HCl	0.070
polysorbate 80	0.050
glycerin	2.000
hydroxypropyl methyl cellulose	1.000
sodium chloride	0.900
ethylenediamine tetraacetic acid	0.050
benzalkonium chloride	0.020
distilled water	q.s. to vol.

(see page 6, Example III).

Ascertainment of the difference between the prior art and the claims (MPEP 2141.02)

Cramer does not exemplify a composition comprising azelastine and fluticasone.

Finding of prima facie obviousness Rational and Motivation (MPEP 2142-2143)

However, one of ordinary skill in the art would have been motivated to make a composition comprising azelastine and fluticasone because Cramer suggests that the combination of a glucocorticoid (i.e. fluticasone) and an antihistamine (i.e. azelastine) provide improved relief of symptoms associated with seasonal or perennial allergic rhinoconjunctivitis.

Thus, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to make a composition comprising azelastine and fluticasone for the purpose of providing intranasal compositions with improved effectiveness in the treatment of seasonal or perennial allergic rhinoconjunctivitis.

Although Cramer does not specifically teach the instantly claimed ester (or salt) forms of fluticasone (i.e. fluticasone valerate or fluticasone propionate), Cramer suggest that fluticasone can be present in a pharmaceutically acceptable salt form. It would have been obvious to one of ordinary skill in the art to utilize fluticasone in any pharmaceutically acceptable salt form that would be therapeutically beneficial to fluticasone. Further, it is known in the art that pharmaceutically acceptable salt forms can include hydrochloride, propionate, valerate salt, etc. (as evidenced by Link et al. US 6,583,180, see column 183 lines 38-67).

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made because the prior art is fairly suggestive of the claimed invention.

7. Claims 22 and 26-27 are rejected under U.S.C. 103(a) as being unpatentable over Cramer (EP 0780127) in view of Modi (US 6,294,153).

Applicant claims a pharmaceutical formulation which comprises azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof and fluticasone, or a pharmaceutically acceptable ester thereof, wherein fluticasone or a pharmaceutically acceptable ester thereof in an amount from about 50micrograms/ml to about 5mg/ml of the formulation.

Determination of the scope and content of the prior art (MPEP 2141.01)

Cramer teaches a nasal spray composition comprising about 0.001 to about 0.2% concentration of a glucocorticosteroid (i.e. beclomethasone, flunisolide, triamcinolone, fluticasone, mometasone, bedusonide and pharmaceutically acceptable salts), 0.01 to about 4% concentration of an antihistamine (i.e. azelastine or pharmaceutically acceptable salt thereof, and an intranasal carrier (see the abstract and page 2 lines 36-45). The composition may contain isotonic agents such as citric acid, boric acid, propylene glycol, etc., thickening agents such as xanthan gum, microcrystalline cellulose,

carboxymethyl cellulose, hydroxypropyl cellulose, etc., humectants such as sorbitol, propylene glycol, polyethylene glycol, etc. and preservatives such as benzyl alcohol, phenylethyl alcohol, and quaternary ammoniums such as benzalkonium chloride (see page 4 lines 50-58 and page 5 lines 1-22). The composition may contain surfactants such as Polysorbate 80, Octoxynol, etc. (see page 5 lines 11-16). The pH of the composition is from about 4.5 to about 9 (see page 2 lines 57-58). The composition may be formulated into a nasal solution (for use as drops or a spray), a nasal suspension, ointment, or gel (see page 3 lines 43-47). Typically the dosage units may be prepared to deliver 0.5mcg to about 100mcg of the glucocorticoid and 5mcg to about 1000mcg of the antihistamine spray (see page 3 lines 58 and page 4 lines 1-2).

Example III discloses an intranasal pharmaceutical composition prepared by combining the following components utilizing conventional mixing techniques, shown below:

Component	Wgt %
triamcinolone acetonide	0.050
azelastine HCl	0.070
polysorbate 80	0.050
glycerin	2.000
hydroxypropyl methyl cellulose	1.000
sodium chloride	0.900
ethylenediamine tetraacetic acid	0.050
benzalkonium chloride	0.020
distilled water	q.s. to vol.

(see page 6, Example III).

Ascertainment of the difference between the prior art and the claims (MPEP 2141.02)

Cramer does not exemplify a nasal composition further comprising a propellant. This deficiency is cured by the teachings of Modi.

Modi teaches aerosol formulations for nasal delivery comprising pharmaceutical agents (i.e. anti-inflammatories, steroids, etc.), water, excipients and a propellant (see the abstract and column 3 lines 30-40). Improved penetration and absorption of the formulations can be achieved by mixing the formulation with propellants such as tetrafluroethane, etc., especially when delivered through aerosol devices (i.e. MDI). (see column 2 lines 5-24).

Finding of prima facie obviousness Rational and Motivation (MPEP 2142-2143)

One of ordinary skill in the art would have been motivated to make a composition further comprising a propellant because Modi suggests that adding propellants to nasal formulations can increase penetration and absorption in the nasal cavity.

Thus, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to make a composition further comprising a propellant for the purpose of increasing penetration of active formulations into the nasal cavity.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made because the prior art is fairly suggestive of the claimed invention.

8. Claims 1-2 and 6 are rejected under U.S.C. 103(a) as being unpatentable over Cramer (EP 0780127) in view of Fassberg et al. (US 6,416,743).

Applicant claims a pharmaceutical formulation which comprises azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof and fluticasone, or a pharmaceutically acceptable ester thereof, wherein fluticasone or a pharmaceutically acceptable ester thereof in an amount from about 50micrograms/ml to about 5mg/ml of the formulation.

Determination of the scope and content of the prior art (MPEP 2141.01)

Cramer teaches a nasal spray composition comprising about 0.001 to about 0.2% concentration of a glucocorticosteroid (i.e. beclomethasone, flunisolide, triamcinolone, fluticasone, mometasone, bedusonide and pharmaceutically acceptable salts), 0.01 to about 4% concentration of an antihistamine (i.e. azelastine or pharmaceutically acceptable salt thereof, and an intranasal carrier (see the abstract and page 2 lines 36-45). The composition may contain isotonic agents such as citric acid, boric acid, propylene glycol, etc., thickening agents such as xanthan gum, microcrystalline cellulose, carboxymethyl cellulose, hydroxypropyl cellulose, etc., humectants such as sorbitol, propylene glycol, polyethylene glycol, etc. and preservatives such as benzyl alcohol, phenylethyl alcohol, and quaternary ammoniums such as benzalkonium chloride (see page 4 lines 50-58 and page 5 lines 1-22). The pH of

the composition is from about 4.5 to about 9 (see page 2 lines 57-58). The composition may be formulated into a nasal solution (for use as drops or a spray), a nasal suspension, ointment, or gel (see page 3 lines 43-47). Typically the dosage units may be prepared to deliver 0.5mcg to about 100mcg of the glucocorticoid and 5mcg to about 1000mcg of the antihistamine spray (see page 3 lines 58 and page 4 lines 1-2).

Example III discloses an intranasal pharmaceutical composition prepared by combining the following components utilizing conventional mixing techniques, shown below:

Component	Wgt %
triamcinolone acetonide	0.050
azelastine HCl	0.070
polysorbate 80	0.050
glycerin	2.000
hydroxypropyl methyl cellulose	1.000
sodium chloride	0.900
ethylenediamine tetraacetic acid	0.050
benzalkonium chloride	0.020
distilled water	q.s. to vol.

(see page 6, Example III).

Ascertainment of the difference between the prior art and the claims (MPEP 2141.02)

Cramer et al. do not teach the instantly claimed formulation comprising azelastine and fluticasone with a particle size of less than 10μm. This deficiency is cured by the teachings of Fassberg et al.

Fassberg et al. teach aerosol formulations for nasal administration comprising 1,1,1,2 tetrafluoroethane and a medicament (see the abstract and column 3 lines 2-7). Examples of the medicaments include antihistamines and

steroids (see column 5 lines 61-66). The particle size of the active compound ranges from 0.1-25μm (see column 6 lines 11-15). The formulation may optionally contain an excipient or surfactant (see the abstract).

Finding of prima facie obviousness Rational and Motivation

(MPEP 2142-2143)

One of ordinary skill in the art would have been motivated to make a composition comprising azelastine and fluticasone with a particle size of less than 10μm because Fassberg et al. nasal compositions comprising antihistamines (e.g. azelastine) or steroids (e.g. fluticasone) can be prepared with a particle size ranging from 0.1-25μm, which overlaps with the instantly claimed particle size of less than 10μm.

Thus, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to make a composition with the instantly claimed particle size range because it is an obvious variation of particle sizes that can be used in the preparation of nasal formulations.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made because the prior art is fairly suggestive of the claimed invention.

9. Claims 1, 25, 28-29 are rejected under U.S.C. 103(a) as being unpatentable over Cramer (EP 0780127) in view of Alfonso et al. (US 6,017,963).

Applicant claims a pharmaceutical formulation which comprises azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof and fluticasone, or a pharmaceutically acceptable ester thereof, wherein fluticasone or a pharmaceutically acceptable ester thereof in an amount from about 50micrograms/ml to about 5mg/ml of the formulation.

Determination of the scope and content of the prior art (MPEP 2141.01)

Cramer teaches a nasal spray composition comprising about 0.001 to about 0.2% concentration of a glucocorticosteroid (i.e. beclomethasone, flunisolide, triamcinolone, fluticasone, mometasone, bedusonide and pharmaceutically acceptable salts), 0.01 to about 4% concentration of an antihistamine (i.e. azelastine or pharmaceutically acceptable salt thereof, and an intranasal carrier (see the abstract and page 2 lines 36-45). The composition may contain isotonic agents such as citric acid, boric acid, propylene glycol, etc., thickening agents such as xanthan gum, microcrystalline cellulose, carboxymethyl cellulose, hydroxypropyl cellulose, etc., humectants such as sorbitol, propylene glycol, polyethylene glycol, etc. and preservatives such as benzyl alcohol, phenylethyl alcohol, and quaternary ammoniums such as benzalkonium chloride (see page 4 lines 50-58 and page 5 lines 1-22). The pH of the composition is from about 4.5 to about 9 (see page 2 lines 57-58). The composition may be formulated into a nasal solution (for use as drops or a spray), a nasal suspension, ointment, or gel (see page 3 lines 43-47). Typically

the dosage units may be prepared to deliver 0.5mcg to about 100mcg of the glucocorticoid and 5mcg to about 1000mcg of the antihistamine spray (see page 3 lines 58 and page 4 lines 1-2).

Example III discloses an intranasal pharmaceutical composition prepared by combining the following components utilizing conventional mixing techniques, shown below:

Component	Wgt %
triamcinolone acetonide	0.050
azelastine HCl	0.070
polysorbate 80	0.050
glycerin	2.000
hydroxypropyl methyl cellulose	1.000
sodium chloride	0.500
ethylenediamine tetraacetic acid	0.050
benzalkonium chloride	0.020
distilled water	q.s. to vol.

(see page 6, Example III).

Ascertainment of the difference between the prior art and the claims (MPEP 2141.02)

Cramer does not teach the instant formulation in the form of an insufflation powder. This deficiency is cured by the teachings of Alfonso et al.

Alfonso et al. teaches intranasal and/or inhalation administration of pharmaceutical agents (see the abstract). The dosage form suitable for intranasal and/or inhalation administration can be in the form of a liquid solution suspension, insufflation powder, etc. for administration as a nasal spray, drop or inhaled fine particles (i.e. insuflation) (see column 3 lines 1-65, column 5 lines 36-45, and column 7 lines 1-26).

Finding of prima facie obviousness Rational and Motivation (MPEP 2142-2143)

One of ordinary skill in the art would have been motivated to make the instant composition in the form of an insufflation powder because Alfonso et al. suggest the nasal compositions in the form of a spray, droplet, insufflation powder, etc.

Thus, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to make the instant composition in the form of an insufflation powder because it is an obvious variation of ways to administer a nasal composition, as suggested Alfonso et al.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made because the prior art is fairly suggestive of the claimed invention.

Response to Arguments

Applicant's arguments filed August 7, 2009 have been fully considered but they are not persuasive.

Applicant argues that Cramer is not fairly suggestive of the instantly claimed combination and that the particular combination instantly claimed is not explicitly mentioned.

This argument is not persuasive. Cramer specifically teaches a nasal spray comprising the combination of a glucocorticoid (i.e. fluticasone) and an antihistamine (i.e. azelastine). There are a limited number of glucocorticoids (six)

and antihistamines (three) recited. It is well within the means for one of ordinary skill in the art to try the instant combination as there are a small number of actives to choose from. Furthermore, disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. *In re Susi*, 440 F.2d 442, 169 USPQ 423 (CCPA 1971).

Next, Applicant argues that the combination of azelastine and fluticasone display unexpected beneficial results. Applicant provides a 1.132 declaration, submitted on July 23, 2009, as evidence of the superior combination.

1.132 Declaration

The declaration provided by Applicant provides a table (Table I) that discloses five compositions, i.e. budesonide alone, azelastine alone, azelastine and budesonide, fluticasone alone, and azelastine and fluticasone. The table also lists the ingredients or excipients added to each composition.

Table II compares the stability of each composition by disclosing the total impurity level of the composition, at the beginning of testing, after one month, and after three months of storage. The impurity level for the composition comprising azelastine and fluticasone appears to remain low and consistently stable throughout the testing period when compared to the composition comprising azelastine and budesonide.

However, this data is not persuasive. First, Applicant has not described what testing method was used, what assay was utilized, and how the impurity level was calculated.

Second, Applicant has not described what the impurity is. It is unclear if the impurity arises from the active, excipients, formulations, etc.

Third, Applicant did not test against the closest prior art examples, described in Cramer (see Example 3). Example 3 in Cramer discloses a composition comprising azelastine and triamcinolone.

Last, it should be noted in Table I, that the instant composition comprising azelastine and fluticasone contains phenylethyl alcohol (a preservative/ antibacterial), whereas the composition comprising azelastine and budesonide does not. It is well known in the art that a preservative is added to composition to prevent decomposition of a substance and to destroy or inhibit multiplication of microorganisms, which also causes decomposition (as evidence by Dorland's Medical Dictionary, Mosby's Medical Dictionary, and American Heritage Medical Dictionary, see 892 form). It is further known that a preservative increases the shelf life of compositions (as evidenced by Cramer page 5 lines 16-18). Applicant is predicating its unexpected results of the instant formulation by measuring the level of impurity in the formulations when compared compositions with similar actives. However, an extremely critical element is missing from the comparative composition. It is neither unexpected nor surprising that a composition comprising an additional preservative would be capable of keeping

impurity levels lower and increasing shelf life when compared to a composition that does not contain the preservative or a lesser amount of preservative.

Applicant also provided a compilation of statements from 6 medical practitioners that attest to the various advantages and superior results associated with the use of the instant invention. Applicant further argues that there is a long felt need for an improved nasal formulation and that the instant composition, known as DUONASE, is a commercial success.

However, given the deficiencies in the data provided by Applicant, one of ordinary skill in the art cannot accurately ascertain whether any unexpected results have occurred.

Therefore, Applicant's arguments and evidence of nonobviousness are not persuasive.

Conclusion

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory

period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KRISTIE L. BROOKS whose telephone number is (571)272-9072. The examiner can normally be reached on M-F 8:30am-6:00pm Est..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann R. Richter can be reached on (571) 272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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

KB

/Mina Haghighatian/
Primary Examiner, Art Unit 1616

Notice of References Cited	Application/Control No. 10/518,016	Applicant(s)/Patent Under Reexamination LULLA ET AL.	
	Examiner KRISTIE L. BROOKS	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-6,416,743	07-2002	Fassberg et al.	424/45
*	B	US-6,294,153	09-2001	Modi, Pankaj	424/45
*	C	US-6,017,963	01-2000	Alfonso et al.	514/646
*	D	US-6,583,180	06-2003	Link et al.	514/603
	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	EP 0 780 127	06-1997		Cramer	
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	preservative. (n.d.) Dorland's Medical Dictionary for Health Consumers. (2007). Retrieved November 4 2009 from http://medical-dictionary.thefreedictionary.com/preservative.
	V	preservative. (n.d.) The American Heritage® Medical Dictionary. (2007). Retrieved November 4 2009 from http://medical-dictionary.thefreedictionary.com/preservative.
	W	preservative. (n.d.) Mosby's Medical Dictionary, 8th edition. (2009). Retrieved November 4 2009 from http://medical-dictionary.thefreedictionary.com/preservative
	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.

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10518016	LULLA ET AL.
	Examiner	**Art Unit**
	KRISTIE L BROOKS	1616

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

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

CLAIM		DATE								
Final	Original	09/23/2008	01/21/2009	10/29/2009						
	1	✓	✓	✓						
	2	✓	✓	✓						
	3	✓	✓	-						
	4	✓	✓	✓						
	5	✓	✓	-						
	6	✓	✓	✓						
	7	✓	✓	✓						
	8	✓	✓	✓						
	9	✓	✓	✓						
	10	✓	✓	✓						
	11	✓	✓	✓						
	12	✓	✓	✓						
	13	✓	✓	✓						
	14	✓	✓	✓						
	15	✓	✓	✓						
	16	✓	✓	✓						
	17	✓	✓	✓						
	18	✓	✓	✓						
	19	✓	✓	✓						
	20	✓	✓	✓						
	21	✓	✓	✓						
	22	✓	✓	✓						
	23	N	N	-						
	24	N	N	-						
	25	✓	✓	✓						
	26	✓	✓	✓						
	27	✓	✓	✓						
	28	✓	✓	✓						
	29	✓	✓	✓						
	30	✓	✓	✓						
	31	✓	✓	-						
	32	✓	✓	-						
	33	✓	✓	-						
	34	✓	✓	-						
	35	✓	✓	✓						
	36	✓	✓	✓						

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10518016	LULLA ET AL.
	Examiner	Art Unit
	KRISTIE L BROOKS	1616

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

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

CLAIM		DATE								
Final	Original	09/23/2008	01/21/2009	10/29/2009						
	37	✓	✓	✓						
	38	✓	✓	✓						
	39	✓	✓	-						
	40	✓	✓	-						
	41	✓	✓	-						
	42	✓	✓	-						
	43	✓	-	-						
	44	✓	✓	✓						
	45	✓	✓	✓						
	46	N	N	-						
	47	N	N	-						
	48	N	N	-						
	49	N	N	-						
	50	N	N	-						
	51		N	-						
	52		N	-						
	53			✓						
	54			✓						
	55			✓						
	56			✓						

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10518016	LULLA ET AL.
	Examiner	Art Unit
	KRISTIE L BROOKS	1616

SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
East Search	11/4/2009	KB
East Search	11/6/2009	KB

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	0	cramer.in. nasal psray	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/06 12:58
L2	5	cramer.in. nasal spray	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/06 12:58
L3	617	(steroid or glucocorticoid) (salt with (propionate and valerate))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/06 14:44
L4	56	(steroid or glucocorticoid).ab. (salt with (propionate and valerate))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/06 14:44
L5	2	"6787532".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/06 15:25
L6	5	"4335121".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/06 15:34
L7	2	"5164194".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/06 15:34
S1702	35	nasal.ti. spray.ab. (particle with size)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 13:20
S1703	13	nasal.ti. spray.ab. (particle with size) active	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 13:20

S1704	7	nasal.ti. spray.ab. (particle with size) (fluticasone or azelastine)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 13:22
S1705	14	nasal.ti. liquid spray (particle with size) (fluticasone or azelastine)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 13:22
S1706	2	nasal.ti. spray.ti. (particle with size) (fluticasone or azelastine)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 13:23
S1707	23	nasal.ti. spray (particle with size) (fluticasone or azelastine)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 13:23
S1708	79	nasal.ti. spray (particle with size) (fluticasone or azelastine or antihistamine or steroid or glucocorticoid)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 13:24
S1709	63	nasal.ti. spray (particle with size) (fluticasone or azelastine or antihistamine or steroid or glucocorticoid) liquid	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 13:24
S1710	48	nasal.ti. spray (particle with size) (fluticasone or azelastine or antihistamine or steroid or glucocorticoid) aqueous	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 13:24
S1711	197	nasal.ab. spray (particle with size) (fluticasone or azelastine or antihistamine or steroid or glucocorticoid) aqueous	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 13:29
S1712	38	nasal.ab. spray.ab. (particle with size) (fluticasone or azelastine or antihistamine or steroid or glucocorticoid) aqueous	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 13:30
S1713	197	nasal.ab. spray (particle with size) (fluticasone or azelastine or antihistamine or steroid or glucocorticoid) aqueous	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 13:32

S1714	153	nasal.ab. spray (particle with size) (fluticasone or azelastine or antihistamine or steroid or glucocorticoid or active) (aqueous with nasal)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 13:32
S1715	51	nasal.ti. spray (particle with size) (fluticasone or azelastine or antihistamine or steroid or glucocorticoid or active) (aqueous with nasal)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 13:32
S1716	15	nasal.ti. spray (particle with size with active) (fluticasone or azelastine or antihistamine or steroid or glucocorticoid or active) (aqueous with nasal)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 13:33
S1717	491	(nasal with spray) (particle with size with active) (fluticasone or azelastine or antihistamine or steroid or glucocorticoid or active) ((aqueous or solution or gel) with nasal)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 13:37
S1718	111	(nasal with spray) (particle with size with active with nasal) (fluticasone or azelastine or antihistamine or steroid or glucocorticoid or active) ((aqueous or solution or gel) with nasal)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 13:37
S1719	6	(nasal with spray) (particle with size with active with nasal) (fluticasone or azelastine) ((aqueous or solution or gel) with nasal)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 13:38
S1720	79	(nasal with spray) (particle with size with active with nasal) (fluticasone or azelastine or antihistamine or anti-histamine or steroid or glucocorticosteroid) ((aqueous or solution or gel) with nasal)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 13:39
S1721	81	(particle with size with active with nasal) (fluticasone or azelastine or antihistamine or anti-histamine or steroid or glucocorticosteroid) ((aqueous or solution or gel) with nasal)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 13:39
S1722	3164	(particle with size with active) (fluticasone or azelastine or antihistamine or anti-histamine or steroid or glucocorticosteroid)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 13:39

S1723	213	(particle with size with active) (fluticasone or azelastine or antihistamine or anti-histamine or steroid or glucocorticosteroid) (aqueous with nasal)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 13:40
S1724	0	(particle with size with active) (fluticasone or azelastine or antihistamine or anti-histamine or steroid or glucocorticosteroid) (aqueous near 1nasal)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 13:40
S1725	14	(particle with size with active) (fluticasone or azelastine or antihistamine or anti-histamine or steroid or glucocorticosteroid) (aqueous near1 nasal)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 13:40
S1726	2	"6391340".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 13:42
S1727	87	(particle with size with active) (fluticasone or azelastine or antihistamine or anti-histamine or steroid or glucocorticosteroid) nasal.ab. (solution or aquoues or gel)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 13:44
S1728	91	(particle with size with active) (fluticasone or azelastine or antihistamine or anti-histamine or steroid or glucocorticosteroid) nasal.ab. (solution or aqueous or gel)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 13:44
S1729	366	nasal (fluticasone with (proprionate or valerate))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 15:31
S1730	366	nasal (fluticasone with (proprionate or valerate)) fluticasone	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 15:32
S1731	18	nasal (fluticasone with (proprionate or valerate)) fluticasone.ab.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 15:32

S1732	1	nasal (fluticasone with (proprionate)) (fluticasone with valerate)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 15:34
S1733	224	nasal (fluticasone with (propionate)) (fluticasone with valerate)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 15:34
S1734	49	nasal (fluticasone with (propionate)) (fluticasone with valerate) fluticasone.clm.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 15:35
S1735	10	nasal (fluticasone near2 (propionate)) (fluticasone near2 valerate) fluticasone	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 15:35
S1736	8	nasal (fluticasone near (propionate)) (fluticasone near2 valerate) fluticasone	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 15:36
S1737	1	nasal (fluticasone near (propionate)) (fluticasone near valerate) fluticasone	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 15:37
S1738	203	nasal (fluticasone near ester) propionate	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 15:37
S1739	95	nasal (fluticasone near ester) propionate fluticasone.clm.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 15:37
S1740	1	nasal (fluticasone near valerate) fluticasone.clm.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 16:44
S1741	2	nasal (fluticasone near valerate) fluticasone	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 16:44

S1742	45	nasal (fluticasone) (valerate near salt)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 16:44
S1743	2	nasal (fluticasone with salt) (valerate near salt)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 16:50
S1744	3	(fluticasone with salt) (valerate near salt)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 16:50
S1745	18	(fluticasone near valerate)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 16:56
S1746	1355	(salt near valerate)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 16:59
S1747	387	(steroid or glucocorticoid or corticosteroid) (salt near valerate)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 17:00
S1748	318	(steroid or glucocorticoid or corticosteroid) (salt near valerate) nasal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 17:00
S1749	52	(steroid or glucocorticoid or corticosteroid) (salt near valerate) nasal ((steroid or glucocorticoid or corticosteroid) with salt)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 17:01
S1750	52	(steroid or glucocorticoid or corticosteroid or fluticasone) (salt near valerate) nasal ((steroid or glucocorticoid or corticosteroid) with salt)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 17:01
S1751	45	(fluticasone) (salt near valerate) nasal	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 17:12

S1752	18	(fluticasone adj valerate)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 17:19
S1753	2	(fluticasone with valeric)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 17:20
S1754	63	(steroid with valeric)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 17:21
S1755	38	(steroid with valeric) salt	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 17:21
S1756	138	(fluticasone with salt) valerate	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 17:24
S1757	55	(fluticasone with salt) valerate fluticasone.clm.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 17:24
S1758	2	"6770594".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 18:05
S1759	264	baur.in. peter.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 18:17
S1760	29	baur.in. peter.in. sulfate	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 18:17
S1761	23	baur.in. peter.in. sulfate alkyl ether	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2009/11/04 18:17

11/6/2009 3:36:18 PM

PTO/SB/08a (06-09)
Approved for use through 07/31/2009. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	10518016
Filing Date	2005-07-06
First Named Inventor	Amar Lulla
Art Unit	1616
Examiner Name	Kristie Latrice Brooks
Attorney Docket Number	PAC/20632 US (4137-04700)

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
/K.B./	1	6787532	B2	2004-09-07	Biggadike, et al.	

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

U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
/K.B./	1	20040242638	A1	2004-12-02	Yanni, et al.	
/K.B./	2	20050192261	A1	2005-09-01	Jost-Price, et al.	
/K.B./	3	20060228306	A1	2006-10-12	Lane	

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

FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
/K.B./	1	1519731	EP	B1	2009-04-15	Cipla, Ltd.		☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	10518016
	Filing Date	2005-07-06
	First Named Inventor	Amar Lulla
	Art Unit	1616
	Examiner Name	Kristie Latrice Brooks
	Attorney Docket Number	PAC/20632 US (4137-04700)

/K.B./	2	2072051	EP	A1	2009-06-24	Cipla, Ltd.		☐
/K.B./	3	2389530	GB	A	2003-12-17	Cipla, Ltd.		☐
/K.B./	4	2003105856	WO	A1	2003-12-24	Cipla Limited		☐

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

NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
/K.B./	1	Foreign communication from the priority application - International Search Report, PCT/GB03/02557, September 17, 2003, 3 pages.	☐
/K.B./	2	Foreign communication from the priority application - International Preliminary Examination Report, PCT/GB03/02557, August 26, 2004, 6 pages.	☐
/K.B./	3	Foreign communication from a related counterpart application - Examination Report, EP Application 03738280.1, November 10, 2005, 4 pages.	☐
/K.B./	4	Foreign communication from a related counterpart application - Examination Report, EP Application 03738280.1, July 18, 2007, 5 pages.	☐
/K.B./	5	Applicants response to foreign communication - EP 03738280.1, May 22, 2006, 36 pages.	☐
/K.B./	6	Applicants response to foreign communication - EP 03738280.1, January 18, 2008, 17 pages.	☐

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	10518016
	Filing Date	2005-07-06
	First Named Inventor	Amar Lulla
	Art Unit	1616
	Examiner Name	Kristie Latrice Brooks
	Attorney Docket Number	PAC/20632 US (4137-04700)

EXAMINER SIGNATURE			
Examiner Signature	/Kristie Brooks/	Date Considered	11/06/2009

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

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

PTO/SB/08a (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	10518016
Filing Date	2005-07-06
First Named Inventor	Amar Lulla
Art Unit	1616
Examiner Name	Kristie Latrice Brooks
Attorney Docket Number	PAC/20632 US (4137-04700)

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
/K.B./	1	4335121		1982-06-15	Phillipps, et al.	
/K.B./	2	5164194		1992-11-17	Hettche	

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

U.S.PATENT APPLICATION PUBLICATIONS Remove

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

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

FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
/K.B./	1	3836579	DE	A1	2009-08-07	Asta Pharma AG		☐

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

NON-PATENT LITERATURE DOCUMENTS Remove

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	10518016
Filing Date	2005-07-06
First Named Inventor	Amar Lulla
Art Unit	1616
Examiner Name	Kristie Latrice Brooks
Attorney Docket Number	PAC/20632 US (4137-04700)

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
/K.B./	1	MAY, PERCY, et al., "May's Chemistry of Synthetic Drugs," Fifth Edition, 1964, pages 12-17, Longmans.	☐

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

EXAMINER SIGNATURE

Examiner Signature	/Kristie Brooks/	Date Considered	11/06/2009

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

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

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	10518016
Filing Date	2005-07-06
First Named Inventor	Amar Lulla
Art Unit	1616
Examiner Name	Kristie Latrice Brooks
Attorney Docket Number	PAC/20632 US (4137-04700)

U.S.PATENTS Remove

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

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

U.S.PATENT APPLICATION PUBLICATIONS Remove

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

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

FOREIGN PATENT DOCUMENTS Remove

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

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

NON-PATENT LITERATURE DOCUMENTS Remove

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	10518016
	Filing Date	2005-07-06
	First Named Inventor	Amar Lulla
	Art Unit	1616
	Examiner Name	Kristie Latrice Brooks
	Attorney Docket Number	PAC/20632 US (4137-04700)

	1	ABPI Compendium of Data Sheets and Summaries of Product Characteristics, 1999-2000, Cover page, pg. 43 and Index Page 1882, Datapharm Publications Limited, London, Great Britain.	☐
	2	DYKEWICZ, MARK S., et al., "Diagnosis and Management of Rhinitis: Complete Guidelines of the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology," Annals of Allergy, Asthma, & Immunology, Vol. 81, November (Part II) 1998, pgs. 478 - 518.	☐
	3	Foreign communication from a related counterpart application - Notice of Opposition, EP Application 03738280.1, February 22, 2010, 22 pages.	☐

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

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

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

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	10518016
	Filing Date	2005-07-06
	First Named Inventor	Amar Lulla
	Art Unit	1616
	Examiner Name	Kristie Latrice Brooks
	Attorney Docket Number	PAC/20632 US (4137-04700)

CERTIFICATION STATEMENT

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

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

OR

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

☐ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ None

SIGNATURE

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

Signature	/Rodney B. Carroll/	Date (YYYY-MM-DD)	2010-03-22
Name/Print	Rodney B. Carroll	Registration Number	39,624

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

Privacy Act Statement

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

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

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

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

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

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

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

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

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

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

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

Electronic Acknowledgement Receipt

EFS ID:	7244550
Application Number:	10518016
International Application Number:	
Confirmation Number:	4912
Title of Invention:	Combination of azelastine and steroids
First Named Inventor/Applicant Name:	Amar Lulla
Customer Number:	30652
Filer:	Rodney B. Carroll/Linda Kerrick
Filer Authorized By:	Rodney B. Carroll
Attorney Docket Number:	PAC/20632 US (4137-04700)
Receipt Date:	22-MAR-2010
Filing Date:	06-JUL-2005
Time Stamp:	19:14:07
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Information Disclosure Statement (IDS) Filed (SB/08)	032210_IDSForm.pdf	774636 bdd5452b1677a439adfde43818fe08352fcb0f02	no	4

Warnings:	
Information:	000653

A U.S. Patent Number Citation or a U.S. Publication Number Citation is required in the Information Disclosure Statement (IDS) form for autoloading of data into USPTO systems. You may remove the form to add the required data in order to correct the Informational Message if you are citing U.S. References. If you chose not to include U.S. References, the image of the form will be processed and be made available within the Image File Wrapper (IFW) system. However, no data will be extracted from this form. Any additional data such as Foreign Patent Documents or Non Patent Literature will be manually reviewed and keyed into USPTO systems.

2	NPL Documents	ABPICompendium.pdf	265265 9b2dff2b70518ad021bc37dea2a77ad940d13d5a	no	3
Warnings:					
Information:					
3	NPL Documents	DYKEWICZ_Diagnosis.pdf	2960328 2aec2c03df322c12f2be6c25c4307585bc325fff	no	41
Warnings:					
Information:					
4	NPL Documents	022210_NoticeofOpposition_EP03738280.pdf	556289 c31a17611e16e4f3cc33c7a4937f46564a130e42	no	22
Warnings:					
Information:					
		Total Files Size (in bytes):	4556518		

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

PTO/SB/08a (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	10518016
Filing Date	2005-07-06
First Named Inventor	Amar Lulla
Art Unit	1616
Examiner Name	Kristie Latrice Brooks
Attorney Docket Number	PAC/20632 US (4137-04700)

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	4335121		1982-06-15	Phillipps, et al.	
	2	5164194		1992-11-17	Hettche	

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

U.S.PATENT APPLICATION PUBLICATIONS Remove

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

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

FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	3836579	DE	A1	2009-08-07	Asta Pharma AG		☐

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

NON-PATENT LITERATURE DOCUMENTS Remove

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	10518016
	Filing Date	2005-07-06
	First Named Inventor	Amar Lulla
	Art Unit	1616
	Examiner Name	Kristie Latrice Brooks
	Attorney Docket Number	PAC/20632 US (4137-04700)

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	MAY, PERCY, et al., "May's Chemistry of Synthetic Drugs," Fifth Edition, 1964, pages 12-17, Longmans.	☐

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

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

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

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	10518016
	Filing Date	2005-07-06
	First Named Inventor	Amar Lulla
	Art Unit	1616
	Examiner Name	Kristie Latrice Brooks
	Attorney Docket Number	PAC/20632 US (4137-04700)

CERTIFICATION STATEMENT

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

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

OR

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

☐ See attached certification statement.

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

☐ None

SIGNATURE

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

Signature	/Rodney B. Carroll/	Date (YYYY-MM-DD)	2009-08-07
Name/Print	Rodney B. Carroll	Registration Number	39,624

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

Privacy Act Statement

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

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

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

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

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

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

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

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

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

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

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

Electronic Patent Application Fee Transmittal

Application Number:	10518016
Filing Date:	06-Jul-2005
Title of Invention:	Combination of azelastine and steroids
First Named Inventor/Applicant Name:	Amar Lulla
Filer:	Rodney B. Carroll/Linda Kerrick
Attorney Docket Number:	PAC/20632 US (4137-04700)

Filed as Large Entity

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

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

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

Electronic Acknowledgement Receipt

EFS ID:	5850891
Application Number:	10518016
International Application Number:	
Confirmation Number:	4912
Title of Invention:	Combination of azelastine and steroids
First Named Inventor/Applicant Name:	Amar Lulla
Customer Number:	30652
Filer:	Rodney B. Carroll/Linda Kerrick
Filer Authorized By:	Rodney B. Carroll
Attorney Docket Number:	PAC/20632 US (4137-04700)
Receipt Date:	07-AUG-2009
Filing Date:	06-JUL-2005
Time Stamp:	16:32:07
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$180
RAM confirmation Number	2537
Deposit Account	501515
Authorized User	

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

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Foreign Reference	DE03836579A1.pdf	487024 3372bfc1f0c3f500b27783b8def60f2cd7faae4c	no	6
Warnings:					
Information:					
2	NPL Documents	MAY_MaysChemistry.pdf	339832 e415b81ac737a94238be6ddd2d3fdcfe0a6ef5bb	no	4
Warnings:					
Information:					
3	Information Disclosure Statement (IDS) Filed (SB/08)	080709_IDSForm.pdf	774042 f3178d5d1a156675b59014299c75544a19e98185	no	4
Warnings:					
Information:					
4	Fee Worksheet (PTO-875)	fee-info.pdf	30161 54050b2752aae4c93908bea219d8aa84b1953278	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	1631059		

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

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

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

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

(19) BUNDESREPUBLIK DEUTSCHLAND

DEUTSCHES PATENTAMT

(12) **Offenlegungsschrift**

(11) **DE 3836579 A1**

(51) Int. Cl. 4:
A61K 31/55
A 61 K 31/50

(21) Aktenzeichen: P 38 36 579.0
(22) Anmeldetag: 27. 10. 88
(43) Offenlegungstag: 24. 5. 89

DE 3836579 A1

(30) Innere Priorität: (32) (33) (31)
13.11.87 DE 37 38 681.6

(71) Anmelder:
Asta Pharma AG, 6000 Frankfurt, DE

(72) Erfinder:
Hettche, Helmut, Dr., 6057 Dietzenbach, DE

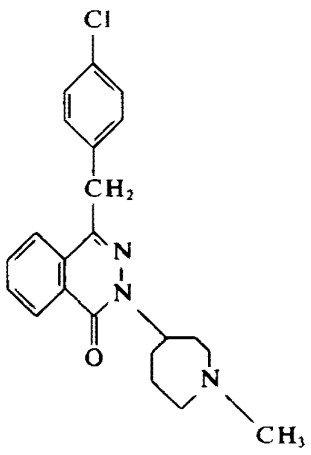
(54) Azelastin enthaltende Arzneimittel zur Anwendung in der Nase und/oder am Auge

Arzneimittel zur nasalen Anwendung oder zur Anwendung am Auge, welches als Wirkstoff Azelastin enthält, wobei das Azelastin auch in Form eines physiologisch verträglichen Salzes vorliegen kann.

DE 3836579 A1

Beschreibung

Azelastin ist ein Phthalazinon-Derivat folgender Strukturformel:



Die chemische Bezeichnung ist: 4-(4-Chlorbenzyl)-2-(perhydro-1-methyl-azepin-4-yl)-1-(2H)phthalazinon. Azelastin wird insbesondere zur Asthmaprophylaxe eingesetzt. Azelastin hat ebenfalls antiallergische und antihistaminische Eigenschaften, siehe deutsches Patent Nr. 21 64 058.

Es wurde nun gefunden, daß Azelastin und dessen physiologisch verträgliche Salze besonders vorteilhafte und überraschende Wirkungen aufweisen, wenn die Applikation entsprechender Zubereitungen in die Nase und/oder den Bindehautsack des Auges erfolgt.

So wird eine Beseitigung beziehungsweise deutliche Linderung nicht nur bei der allergisch bedingten Rhinitis, sondern auch bei dem normalen banalen Schnupfen (beispielsweise durch Rhino-Viren verursacht) sowie dem vasomotorischen Schnupfen und den hierdurch ausgelösten Krankheitssymptomen erzielt.

Überraschend ist hierbei, daß bei der lokalen nasalen Anwendung auch eine günstige Wirkung auf die Schleimhaut des Auges eintritt (Beseitigung beziehungsweise Linderung der Augenrötung und des Augenjuckens), so daß sich häufig eine zusätzliche Anwendung von Augentropfen erübrigt.

Weitere Indikationen für die erfindungsgemäße Applikation/Anwendung sind beispielsweise: nicht spezifische Konjunctivitis, allergisch bedingte Konjunctivitis, allergisches Lidödem, katarrhliche Zustände im Auge oder der Nase, Coryza.

Bei der erfindungsgemäßen Anwendung wird außerdem überraschend die bei anderen Applikationen auftretende Müdigkeit nicht beobachtet.

Weiterhin besitzt Azelastin einen außerordentlich durchdringenden bitteren Geschmack, der bis jetzt jede orale Applikation von Azelastin-Lösungen verhindert hat, da solche Azelastin-Lösungen beziehungsweise Suspensionen von den Patienten abgelehnt werden.

Der Grad des Bittergeschmacks ist so intensiv, daß er sogar noch in einer Verdünnung von $1 : 10^6$ unangenehm wahrgenommen wird. Überraschend zeigte sich im Probandenversuch, daß beim Einsprühen der Azelastin-Zubereitungen gemäß der Erfindung in die Nase dieser bittere Geschmack nicht mehr in Erscheingung tritt, so daß es auf diese Weise möglich ist, Lösungen

oder Suspensionen von Azelastin und dessen Salzen ohne Geschmacksbeeinträchtigung nasal zu applizieren. Auch beim Hinunterlaufen der eingesprühten Azelastin-Lösung beziehungsweise Suspension in den Rachenraum ist der bittere Geschmack kaum noch wahrnehmbar.

Aufgabe der Erfindung ist also die Bereitstellung eines gut verträglichen und verbesserten Mittels auf der Basis von Azelastin beziehungsweise dessen Salzen zur Behandlung sowohl des allergisch bedingten wie auch des vasomotorischen und durch Rhino-Viren verursachten Schnupfens und dessen Begleiterscheinungen.

Die bevorzugte Ausführungsform der Erfindung stellt eine sterile und haltbare wäßrige Lösung von Azelastin beziehungsweise dessen Salzen dar, die in Form von Tropfen, Salben, Cremes, Gelen, Einblaspulvern oder in einer ganz besonders bevorzugten Ausführung in Form eines Sprays (vorzugsweise Nasenspray) angewendet wird, wobei das Spray durch Verwendung einer üblichen Sprühquetschflasche oder eines Pumpzerstäubers erzeugt werden kann. Weiterhin sind Druckgasaerosole möglich. Beispielsweise sollen pro Einzelsprühstoß 0,03 bis 3 mg Azelastin-Base freigesetzt werden.

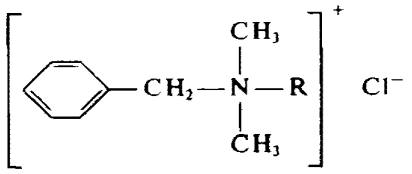
Durch Anwendung von Nasentropfen oder eines Nasensprays ist die für die Behandlung des Schnupfens erfoderliche Dosierung des Azelastins um etwa eine Zehnerpotenz niedriger und damit die Häufigkeit des Auftretens von Nebenwirkungen wesentlich geringer als bei der Anwendung von Azelastin in oral einzunehmenden Darreichungsformen wie Tabletten oder Säften, durch die der gesamte Körper mit der Wirksubstanz überschwemmt wird. Insbesondere bei der Behandlugn einer banalen Krankheit wie des Schnupfens ist eine niedrige Nebenwirkungsrate absolut geboten und erforderlich und stellt daher einen erheblichen medizinischen Fortschritt dar.

Als Lösungsmittel für die erfindungsgemäßen Zubereitungen kommen vorzugsweise in Frage: Wasser, gesättigte aliphatische ein- und mehrwertige Alkohole mit 2—3 C-Atomen (zum Beispiel Ethanol, Isopropanol, 1,2-Propylenglykol, Glycerin), flüssige Polyglykole (Mol-Gewicht 200 bis 600).

Vorzugsweise kommt als Lösungsmittel Wasser in Frage beziehungsweise Gemische von Wasser mit anderen physiologisch verträglichen Lösungsmitteln (beispielsweise den zuvor genannten), wobei die Menge an letzteren in der wäßrigen Mischung nicht über 15 Gew.-% betragen soll.

Die Lösungen beziehungsweise Zubereitungen enthalten vorzugsweise Konservierungsmittel und Stabilisatoren. Als solche kommen zum Beispiel in Frage: Ethylendiamintetraessigsäure (Editinsäure) und deren Alkalisalze (zum Beispiel Dialkalisalze wie Dinatriumsalz, Calciumsalz, Calcium-Natriumsalz), p-Hydroxybenzoesäure-Niederalkylester, Chlorhexidin (zum Beispiel in Form des Acetats oder Gluconats), Phenylquecksilberborat. Weiterhin kommen beispielsweise in Frage Natrium-(2-ethylmercurithio)-benzoat; als "Thiomersal" allgemein bekannt, das in den erfindungsgemäßen Zubereitungen in einer Menge von 0,001 bis 0,05, vorzugsweise von 0,005 bis 0,02, zum Beispiel 0,01% (Gewicht/Volumen bei flüssigen Zubereitungen, sonst Gewicht/Gewicht) vorhanden sein kann. Weitere geeignete Konservierungsmittel sind: pharmazeutisch verwendbare quartäre Ammoniumverbindungen, zum Beispiel Cetylpyridiniumchlorid, Tetradecyltrimethylammoniumbromid, allgemein als "Cetrimid" bekannt, Benzyldimethyl--[2-[2-[p-(1,1,3,3-tetramethylbutyl)]-phenoxy]ät-

hoxy]-ammoniumchlorid, allgemein als "Benzethoniumchlorid" bekannt, und Myristyl-γ-pikoliniumchlorid, wobei jede dieser Verbindungen in einer Konzentration von 0,002 bis 0,05, zum Beispiel 0,02% (Gewicht/Volumen bei flüssigen Zubereitungen, sonst Gewicht/Gewicht) verwendet werden kann. Die bevorzugten Konservierungsmittel unter den quartären Ammoniumverbindungen sind jedoch die Alkylbenzyldimethylammoniumchloride und Mischungen von diesen, zum Beispiel die allgemein als "Benzalkoniumchlorid" bekannten Verbindungen. Diese letztere besteht aus einer Mischung der Verbindungen der Formel



in der R eine Alkylgruppe mit der Formel C_nH_{2n+1}, wobei n eine ganze Zahl von 8 bis 18 bedeutet, darstellt. Besonders bevorzugt wird die Verwendung einer Mischung von Verbindungen, in denen n 10 bis 14 bedeutet, und insbesondere die spezielle Verbindung, in welcher $R = C_{12}H_{25}$ ist. "Benzalkoniumchlorid" und die Verbindungen der obigen Formel können in Konzentrationen von 0,005 bis 0,10, vorzugsweise von 0,005 bis 0,05, zum Beispiel von 0,01% (Gewicht/Volumen bei flüssigen Zubereitungen, sonst Gewicht/Gewicht) verwendet werden, und sie können gegebenenfalls in Kombination mit 0,2 bis 2,0, zum Beispiel 0,4% (Gewicht/Volumen) von 2-Phenyläthanol verwendet werden.

Die erfindungsgemäßen Zubereitungen (Lösungen, Suspensionen, auch ölige Lösungen beziehungsweise Suspensionen, Salben, Emulsionen, Cremes, Gele, Dosier-Aerosole) enthalten 0,0005 bis 2, vorzugsweise 0,001 bis 1, insbesondere 0,003 bis 0,5% (Gewicht/Gewicht) Azelastin (bezogen auf die freie Azelastin-Base). Liegt das Azelastin als Salz vor, sind diese Mengen entsprechend umzurechnen. Für die Augentropfen kommen dieselben Azelastin-Konzentrationen in Frage wie für die nasalen Formen.

Im Falle von Pulvern beträgt die Konzentration an Azelastin-Base 0,0005 bis 2 Gewichtsprozent, bezogen auf die festen Trägerstoffe.

Bei Lösungen beträgt die Dosierung pro Nasenloch zum Beispiel 0,01 bis 0,2 ml, insbesondere 0,05 bis 0,15 ml, wobei eine solche Dosierung zum Beispiel 1- bis mehrmals, vorzugsweise 1- bis 5mal täglich zu applizieren ist (gegebenenfalls auch stündlich).

Bei der Anwendung am Auge (Augentropfen) beträgt die Dosierung zum Beispiel 1 Tropfen (etwa 0,05 ml) der Lösung oder entsprechende Mengen der halbfesten Zubereitungsformen.

Als Säurekomponente für Salze des Azelastins kommen zum Beispiel in Frage: Halogenwasserstoffsäuren (HCl, HBr), Schwefelsäure, Phosphorsäuren (H_3PO_4, Metaphosphorsäure, Polyphosphorsäuren), Salpetersäure, organische Mono-, Di- oder Tricarbonsäuren von aliphatischen, alicyclischen, aromatischen oder heterocyclischen organischen Säuren (Embonsäure, Zitronensäure, Weinsäure), aliphatische und aromatische Sulfonsäuren (zum Beispiel Camphersulfonsäure).

Die Gesamtmenge an Konservierungsmittel in den Zubereitungen (Lösungen, Salben usw.) beträgt pro 100 ml Lösung/Suspension beziehungsweise 100 g Zubereitung zwischen 0,001 und 0,10, vorzugsweise 0,01 g.

Bei den Konservierungsmitteln kommen für Einzelstoffe zum Beispiel folgende Mengen in Frage:

Thiomersal 0,002 – 0,02%,
Benzalkoniumchlorid 0,002 bis 0,02% (bei Kombination mit Thiomersal ist die Menge Thiomersal zum Beispiel = 0,002 bis 0,005%);
Chlorhexidinacetat beziehungsweise -gluconat 0,01 bis 0,02%;
Phenylquecksilbernitrat, -borat, -acetat 0,002 – 0,004%;
p-Hydroxybenzoesäureester (zum Beispiel Mischung des Methylesters und Propylesters 7 : 3) 0,05 – 0,15, vorzugsweise 0,1%.

Vorzugsweise wird als Konservierungsmittel eine Kombination von Edetinsäure (zum Beispiel als Dinatriumsalz) und Benzalkoniumchlorid verwendet, wobei Edetinsäure in einer Konzentration von 0,05 bis 0,1%, Benzalkoniumchlorid 0,005 bis 0,05%, vorzugsweise in einer Konzentration von 0,1% eingesetzt wird.

Bei Lösungen/Suspensionen handelt es sich stets um Gewichtsprozent/Volumen, bei festen beziehungsweise halbfesten Zubereitungen um Gewichtsprozent/Gewicht der Zubereitung.

Als weitere Hilfsstoffe für die erfindungsgemäßen Zubereitungen kommen beispielsweise in Frage: Polyvinylpyrrolidon, Sorbitanfettsäureester wie Sorbitantrioleat, polyethoxylierte Sorbitanfettsäureester (zum Beispiel polyethoxylierte Sorbitantrioleat), Sorbimacrogololeat, synthetische Amphotenside (Tritone), Ethylenoxidether von Octylphenolformaldehyd-Kondensationsprodukten, Phosphatide wie Lecithin, polyethoxylierte Fette, polyethoxylierte Oleotriglyceride, polyethoxylierte Fettalkohole. Polyethoxyliert bedeutet hierbei, daß die betreffenden Stoffe Polyoxyethylenketten enthalten, deren Polymerisationsgrad im allgemeinen zwischen 2 bis 40, insbesondere zwischen 10 bis 20 liegt. Diese Stoffe dienen vorzugsweise einer Löslichkeitsverbesserung der Azelastinkomponente.

Bei Zubereitungsformen, die Wasser enthalten, können gegebenenfalls zusätzlich Isotonisierungsmittel zugesetzt werden. Als Isotonisierungsmittel kommen zum Beispiel in Betracht: Saccharose, Glucose, Glycerin, Sorbit, 1,2-Propylenglykol, NaCl.

Die Isotonisierungsmittel bewirken die Einstellung der Zubereitungen auf den gleichen osmotischen Druck wie das Nasensekret. Für diesen Zweck ist von diesen Stoffen jeweils soviel zu verwenden, daß beispielsweise im Falle einer Lösung eine Gefrierpunkterniedrigung von 0,50 bis 0,56°C im Vergleich zu reinem Wasser erreicht wird. Bei Beispiel 1 wäre beispielsweise von solchen Stoffen eine solche Menge zu verwenden, die 68 g Natriumchlorid (0,68%) isoosmotisch ist.

Im Beispiel 1 können statt NaCl pro 100 ml Lösung zum Beispiel verwendet werden:
Glucose 1 H_2O 3,81 g; Saccharose 6,35 g; Glycerin 2,2 g; 1,2-Propylenglykol 1,617 g; Sorbit 3,84 g. (Im Falle von Mischungen dieser Stoffe gegebenenfalls entsprechend weniger.)

Den Lösungen können weiterhin Verdickungsmittel, die ein zu schnelles Abfließen der Lösung aus der Nase verhindern und der Lösung eine Viskosität von etwa 1,5 bis 3, vorzugsweise 2 mPa · s verleihen, zugesetzt werden. Als solche Verdickungsmittel kommen zum Beispiel in Frage: Cellulosederivate (zum Beispiel Celluloseether), bei denen die Cellulose-Hydroxygruppen teilweise mit niederen ungesättigten aliphatischen Alkohol-

en und/oder niederen ungesättigten aliphatischen Oxyalkoholen verethert sind (zum Beispiel Methylcellulose, Carboxymethylcellulose, Hydroxypropylmethylcellulose), Gelatine, Polyvinylpyrrolidon, Traganth, Ethoxose (wasserlösliches Binde- und Verdickungsmittel auf Basis von Ethylcellulose), Alginsäure, Polyvinylalkohol, Polyacrylsäure, Pektin und äquivalente Mittel. Falls diese Stoffe saure Gruppen enthalten, kommen auch die entsprechenden physiologisch verträglichen Salze in Frage.

Im Falle der Verwendung von Hydroxy-propylcellulose werden beispielsweise 0,1 Gewichts-% für diesen Zweck verwendet.

Den Zubereitungen können außerdem Puffersubstanzen wie Zitronensäure/Natriumhydrogenphosphat, Borat-Puffer, Phosphate (Natriumdihydrogenorthophosphat, Dinatriumhydrogenphosphat), Tromethamol beziehungsweise äquivalente übliche Puffer zugesetzt werden, um beispielsweise einen pH-Wert der Zubereitung von 6 bis 7,5, vorzugsweise 6,5 bis 7,1 einzustellen.

Die Menge an Zitronensäure beträgt zum Beispiel 0,01 bis 0,14, vorzugsweise 0,04 bis 0,05 g, die Menge an Dinatriumhydrogenphosphat 0,1 bis 0,5, vorzugsweise 0,2 bis 0,3 g pro 100 ml Lösung. Die angegebenen Gewichtsmengen beziehen sich jeweils auf die wasserfreien Substanzen.

Bei den Lösungen und Suspensionen soll die maximale Gesamtkonzentration an Arzneimittel und Puffer weniger als 5%, insbesondere weniger als 2% (Gewicht/Volumen) betragen.

Vorzugsweise wird für die nasale Applikation eine Lösung oder Suspension verwendet, die als Aerosol, das heißt in Form einer feinen Verteilung in Luft oder einem anderen üblichen Trägergas zum Beispiel mittels eines üblichen Pumpzerstäubers appliziert wird.

Es ist jedoch auch eine Applikation als Dosieraerosol möglich. Unter Dosieraerosolen sind Druckpackungen zu verstehen, die das Azelastin beziehungsweise dessen Salze in Form einer Lösung oder Suspension in einem sogenannten Treibmittel enthalten. Als Treibmittel gelten unter Druck stehende flüssige, bei Normaldruck und Raumtemperatur gasförmige chlorierte fluorierte Kohlenwasserstoffe oder Mischungen von verschiedenen chlorierten fluorierten Kohlenwasserstoffen sowie Propan, Butan, Isobutan oder Mischungen dieser untereinander oder mit chlorierten, fluorierten Kohlenwasserstoffen. Die Druckpackung weist ein Dosierventil auf, das bei Betätigung eine definierte Menge der Arzneistofflösung beziehungsweise -suspension freigibt. Durch die anschließend erfolgende schlagartige Verdampfung des Treibmittels wird die Lösung beziehungsweise Suspension von Azelastin in feinste Tröpfchen beziehungsweise Partikelchen zerrissen, die in die Nase gesprüht werden oder für eine Einatmung in die Nase zur Verfügung stehen. Man bedient sich zur Betätigung des Ventils und zur Verbringung der versprühten Suspension in die Nase bestimmter Applikatoren aus Kunststoff. Als Treibmittel kommen aber auch in Frage: CO_2, Distickstoffoxid, Preßluft.

Bei der Applikation als Aerosol kann auch ein üblicher Adapter verwendet werden.

Bei Verwendung von Suspensionen soll die maximale Teilchengröße der festen Stoffe (Azelastin + Hilfsstoffe) nicht größer als 30 µm sein.

Bei der Anwendung in Form eines Einblaspulvers soll die maximale Teilchengröße der Stoffe nicht größer als 20 µm sein.

Es handelt sich hierbei beispielsweise um ein Verstäuben von festem Azelastin oder dessen Salzen. In diesem Fall wird beispielsweise Azelastin beziehungsweise sein Salz mit inerten Trägerstoffen vermischt beziehungsweise auf inerte Trägerstoffe aufgezogen. Als Trägerstoffe kommen zum Beispiel in Frage: Zucker wie Glucose, Saccharose, Lactose, Fructose. Sodann Stärke oder Stärkederivate, Oligosaccharide wie Dextrine, Cyclodextrine und deren Derivate, Polyvinylpyrrolidon, Alginsäure, Tylose, Kieselsäure, Cellulose, Cellulosederivate (zum Beispiel Celluloseether), Zuckeralkohole wie Mannit oder Sorbit, Calciumcarbonat, Calciumphosphat. Die Konzentration von Azelastin beträgt 1 Gewichtsteil Azelastin auf 50 bis 200 000 Gewichtsteile Trägersubstanz (0,0005 bis 2% Azelastin).

Beispiel 1

Nasenspray oder Nasentropfen oder Augentropfen mit 0,1% Azelastinhydrochlorid als Wirkstoff

In 9,00 kg Wasser werden in folgender Reihenfolge gelöst:
10 g Azelastinhydrochlorid, 5 g Edetinsäure-Dinatriumsalz · 2 H_2O, 68 g Natriumchlorid, 1,25 g Alkylbenzyldimethylammoniumchlorid (Benzalkoniumchlorid), 4,38 g Citronensäure, 64,8 g Natriummonohydrogenphosphat · 12 H_2O sowie 10 g Hydroxypropyl-Methylcellulose (Handelsprodukt, zum Beispiel Methocel E4M premium). Die erhaltene Lösung wird mit Wasser auf 10,05 kg = 10 Liter aufgefüllt und nach sorgfältigem Mischen über ein Membranfilter der Porenweite 0,2 µm filtriert, wobei 500 ml Vorlauf verworfen werden. Das Filtrat hat einen pH-Wert von 6,8 ± 0,3. Die Abfüllung erfolgt in Kunststoff-Flaschen, die mit einem üblichen Sprüheinsatz, oder in Kunststoff- beziehungsweise Glasflaschen, die mit einem üblichen Pumpensprüher verschlossen werden. Im letzteren Fall werden zum Beispiel Pumpen mit Nasensprühaufsatz verwendet, die pro Betätigung circa 0,14 ml Lösung versprühen. Damit werden pro Betätigung 0,14 mg Azelastinhydrochlorid in Form der Lösung in die Nase gesprüht.

Füllt man das oben erhaltene Filtrat in für Nasentropfen oder Augentropfen übliche Flaschen mit Tropfpipette ab, so kann die Lösung mittels Tropfpipette in die Nase oder ins Auge geträufelt werden.

Beispiel 2

Nasensalbe mit 0,1% Azelastinhydrochlorid

In einem heizbaren Behälter werden 5 kg Polyoxyethylenstearat (Polyoxyethylen-40-stearat, feste, weiße bis cremefarbene Masse, $D.^{25}$ ca. 1,1, F. 40—44°C, Erstarrungspunkt ca. 41°C), 8 kg Cetylstearylalkohol (Lanette 0), 20 kg weißes Vaselin, 15 kg flüssiges Paraffin und 0,5 kg Siliconöl zusammengeschmolzen. In die Schmelze (Temperatur der Schmelze 80°C) werden 126 g p-Hydroxybenzoesäuremethylester und 53 g p-Hydroxybenzoesäurepropylester gelöst. Anschließend wird eine auf 70°C erwärmte Lösung von 0,1 kg Azelastinhydrochlorid, 140 g p-Hydroxybenzoesäuremethylester und 60 g p-Hydroxybenzoesäurepropylester in 51,021 kg gereinigtem Wasser mit Hilfe eines hochtourigen Rührers einemulgiert und die erhaltene Emulsion bis zum Erkalten gerührt und in regelmäßigen Zeitabständen wiederholt homogenisiert.

Die Abfüllung der Salbe erfolgt in Tuben, die vor dem Gewinde eine röhrenförmige Verlängerung aufweisen und daher zur Applikation der Salbe in die Nase beson-

ders geeignet sind.

Beispiel 3

Dosieraerosol mit einer Abgabe von 0,5 mg Azelastinhydrochlorid pro Hub

In einem geeigneten Kühlbehälter werden circa 8,0 kg eines Gemisches aus 70 Gewichtsteilen Difluordichlormethan und 30 Gewichtsteilen 1,2-Dichlortetrafluorethan auf etwa −55°C abgekühlt. In diesem Gemisch wird bei −55°C eine Mischung aus 0,086 kg vorgekühltem Sorbitantrioleat und 0,8600 kg vorgekühltem Trichlorfluormethan unter Rühren gelöst. In die so erhaltene Lösung werden dann unter intensivem Rühren 0,0688 kg mikronisiertes Azelastinhydrochlorid und 0,0688 kg mikronisierte Lactose portionsweise eingetragen. Durch Zugabe von weiterem, auf etwa −55°C gekühltem Gemisch aus 70 Gewichtsteilen Difluordichlormethan und 30 Gewichtsteilen 1,2-Dichlortetrafluorethan wird das Gesamtgewicht der erhaltenen Suspension auf 9,547 kg gebracht.

Nach dem Verschließen des Kühlbehälters wird die Suspension unter intensivem Rühren erneut auf etwa −55°C abgekühlt. Sie ist danach abfüllfertig.

Unter fortgesetztem Rühren wird die Suspension in übliche geeignete Aluminium-Monobloc-Dosen abgefüllt. Die Monobloc-Dosen werden unmittelbar nach Einfüllung der Suspension mit hierfür üblichen Dosierventilen verschlossen, die pro Ventilbetätigung 0,05 ml Suspension freisetzen. Bei der Betätigung des Ventils werden damit 0,5 mg Azelastinhydrochlorid abgegeben. Die Abgabe erfolgt in Verbindung mit einem üblichen Applikator, der die Einbringung der Wirkungssubstanz in die Nase des Patienten erlaubt.

Beispiel 4

Augentropfen mit 0,05% Azelastinhydrochlorid

140 g Polyvinylalkohol (Handelsname zum Beispiel: Mowiol 26-88/Hoechst AG, Frankfurt 80) werden in 4 Liter kaltes Wasser für Injektionszwecke eingerührt, die Suspension auf 90°C erwärmt und 45 Minuten bei dieser Temperatur belassen. Die erhaltene Lösung wird nach dem Abkühlen mit folgenden Lösungen gemischt: 5 g Azelastinhydrochlorid in 1 Liter Wasser für Injektionszwecke, 0,2 g Phenylquecksilbernitrat in 2 Liter Wasser für Injektionszwecke, 70 g Natriumchlorid in 1 Liter Wasser für Injektionszwecke.

Die Mischung wird durch Zusatz von 0,1 N Natronlauge auf einen pH-Wert von 6,8 eingestellt, mit einer Lösung von 15 g Natriumdihydrogenphosphat · 2 H_2O und 21 g Dinatriumhydrogenphosphat · 2 H_2O in 1 Liter Wasser für Injektionszwecke vermischt und mit Wasser für Injektionszwecke auf 10 Liter aufgefüllt.

Nach sorgfältigem Mischen wird die Lösung durch ein Membranfilter der Porenweite 0,2 µm mit Glasfaservorfilter filtriert und nach Verwerfen eines Vorlaufs von 500 ml unter aseptischen Bedingungen in sterile Augentropfenflaschen abgefüllt.

Patentansprüche

1. Arzneimittel zur nasalen Anwendung oder zur Anwendung am Auge, welches 0,0005 bis 2% (Gewicht/Gewicht) Azelastin enthält, wobei das Azelastin auch in Form eines physiologisch verträglichen Salzes vorliegen kann.
2. Arzneimittel gemäß Anspruch 1, dadurch gekennzeichnet, daß es zur Behandlung von allergisch bedingtem oder vasomotorischem oder durch Rhino-Viren verursachtem Schnupfen beziehungsweise Krankheitssymptomen verwendet wird.
3. Arzneimittel nach einem oder mehreren der vorangegangenen Ansprüche, dadurch gekennzeichnet, daß es ein pharmazeutisch verwendbares Konservierungsmittel in einer Menge von 0,001 bis 0,1% (bei Lösungen — Gewicht pro Volumen der Lösung; bei festen Zubereitungen Gewicht pro Gewicht der Zubereitung) enthält.
4. Arzneimittel nach einem oder mehreren der vorangegangenen Ansprüche, dadurch gekennzeichnet, daß es eine wäßrige Lösung darstellt.
5. Lösung nach einem oder mehreren der vorangegangenen Ansprüche, dadurch gekennzeichnet, daß sie 0,001 bis 0,05% (Gewicht/Volumen Lösung) Natrium-2-(ethylmercurithio)-benzoat oder 0,001 bis 0,1% (Gewicht/Volumen Lösung) Alkylbenzyldimethylammoniumchlorid enthält.
6. Verfahren zur Herstellung eines Arzneimittels zur nasalen Anwendung oder zur Anwendung am Auge, welches 0,0005 bis 2% (Gewicht/Gewicht) Azelastin enthält, wobei das Azelastin auch in Form eines physiologisch verträglichen Salzes vorliegen kann.
7. Verfahren zur Herstellung eines Arzneimittels gemäß Anspruch 1, dadurch gekennzeichnet, daß es zur Behandlung von allergisch bedingtem oder vasomotorischem oder durch Rhino-Viren verursachtem Schnupfen beziehungsweise Krankheitssymptomen verwendet wird.
8. Methode zur Behandlung von Reizzuständen oder Krankheitszuständen der Nase und der Augen durch Applikation eines Arzneimittels, welches Azelastin oder dessen physiologisch verträgliche Salze enthält, in die Nase oder in den Bindehautsack des Auges.
9. Verfahren zur Herstellung von sterilen Azelastin-haltigen Zubereitungen zur Anwendung in der Nase und/oder am Auge, dadurch gekennzeichnet, daß man bei Temperaturen zwischen −55 und +80°C

a) 1 bis 1000 mg Azelastin oder ein physiologisch verträgliches Salz des Azelastins in 50 bis 200 ml Wasser, welches gegebenenfalls bis zu 15 Gewichts-% weitere, mit Wasser mischbare verträgliche Lösungsmittel enthalten kann, unter gleichzeitigem oder nachfolgendem Zusatz von
1 bis 400 mg Konservierungsstoffen,
50 bis 4000 mg Stabilisierungsmitteln beziehungsweise löslichkeitsverbessernden Stoffen
auflöst und gegebenenfalls die Lösung mittels Puffer auf einen pH-Wert von 6,5 bis 7,1 einstellt sowie gegebenenfalls Isotonisierungsmittel zusetzt; oder

b) die in a) erhaltene Lösung durch Zusatz von 0,5 bis 10 g Verdickungsmittel in ein Gel überführt; oder

c) 7,5 mg bis 10 g Azelastin oder ein physiologisch verträgliches Salz des Azelastins in 400 bis 900 ml Wasser unter gleichzeitigem oder nachfolgendem Zusatz von 10—200 mg Konservierungsstoffen auflöst, die Lösung in 100—600 g einer Schmelze aus Kohlenwasser-

stoffgemischen und/oder Silikonen und/oder anderen fettartigen Bestandteilen (Fetten, Fettalkoholen) sowie Emulgatoren einemulgiert und die erhaltene Emulsion homogenisiert und dabei abkühlt bis auf Raumtemperatur; oder

d) 0,05 bis 100 g Azelastin oder ein physiologisch verträgliches Salz des Azelastins in 5 bis 10 kg eines Gemisches aus chlorierten fluorierten Kohlenwasserstoffen und/oder Kohlenwasserstoffen unter Zusatz von 25 bis 150 g Sorbitantrioleat dispergiert und die erhaltene Suspension in Dosen abfüllt, die mit Dosierventilen verschlossen sind beziehungsweise werden, welche pro Betätigung 0,025 bis 0,1 ml der Suspension freisetzen; oder

e) 5 mg bis 10 g Azelastin oder ein physiologisch verträgliches Salz des Azelastins mit 500 bis 1000 g eines physiologisch inerten Trägerstoffes mischt beziehungsweise die Lösung der genannten Menge Azelastin oder eines physiologisch verträglichen Salzes von Azelastin gegebenenfalls portionsweise mit der genannten Menge inertem Trägerstoff mischt und nachfolgend das Lösungsmittel wieder abdampft und die erhaltene Mischung in einer Menge von 20 bis 1000 mg in Hartgelatinekapseln oder Tütchen abfüllt.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Amar Lulla, *et al.*

Serial No.: 10/518,016

Filed: July 6, 2005

For: COMBINATION OF AZELASTINE AND STEROIDS

§
§ Group Art Unit: 1616
§
§ Examiner: Kristie Latrice Brooks
§
§ Confirmation No.: 4912
§
§
§

Mail Stop: Amendment
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

CERTIFICATE OF EFS-WEB FILING

I hereby certify that this correspondence is being electronically filed at the USPTO website to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria VA 22313-1450 on 7/23/2009

Edith Shek

Edith S. Shek

AMENDMENTS AND RESPONSE TO OFFICE ACTION DATED JANUARY 23, 2009

Dear Sir:

In response to the Office Action dated January 23, 2009, Applicants respectfully request the following amendments to the above-identified application as follows. The changes made are shown by underlining the added text and striking through the deleted text.

Amendments to the Claims are reflected in the listing of claims, which begins on page 2 of this paper.

Remarks/Arguments begin on page 10 of this paper.

AMENDMENTS TO THE CLAIMS

Listing of Claims:

1. (Currently Amended) A pharmaceutical formulation which comprises azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, and fluticasone or a pharmaceutically acceptable ester thereof~~a steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof~~, which contains the fluticasone or a pharmaceutically acceptable ester thereof in an amount from about 50 micrograms/ml to about 5 mg/ml of the formulation.

2. (Original) A pharmaceutical formulation according to claim 1, wherein said azelastine is present as azelastine hydrochloride.

3. (Canceled)

4. (Currently Amended) A formulation according to ~~claim 3~~claim 1, wherein the ~~steroid~~ pharmaceutically acceptable ester is ~~beclomethasone propionate, mometasonefuroate, mometasone furoate monohydrate,~~ fluticasone propionate or fluticasone valerate.

5. (Canceled)

6. (Currently Amended) A formulation according to claim 1, wherein the formulation has a particle size of less than ~~about~~ 10 μm.

7. (Currently Amended) A formulation according to claim 1, which is a suspension containing 0.0005 to 2% (weight/weight of the formulation) of azelastine or a pharmaceutically acceptable salt of azelastine, and from 0.5 to 1.5% (weight/weight of the formulation) of fluticasone or a pharmaceutically acceptable ester thereof~~said steroid~~.

8. (Currently Amended) A formulation according to claim 7, which contains from 0.001 to 1% (weight/weight of the formulation) azelastine, or salt thereof, and from 0.5% to 1.5% (weight/weight of the formulation) fluticasone or a pharmaceutically acceptable ester thereof~~steroid~~.

9. (Previously Presented) A formulation according to claim 1, which also contains a surfactant.

10. (Original) A formulation according to claim 9, wherein the surfactant comprises a polysorbate or poloxamer surfactant.

11. (Previously Presented) A formulation according to claim 9, which contains from about 50 micrograms to about 1 milligram of surfactant per ml of the formulation.

12. (Previously Presented) A formulation according to claim 1, which also contains an isotonic agent.

13. (Original) A formulation according to claim 12, wherein the isotonic agent comprises sodium chloride, saccharose, glucose, glycerine, sorbitol or 1,2-propylene glycol.

14. (Previously Presented) A formulation according to claim 1, which also contains at least one additive selected from the group consisting of a buffer, a preservative, a suspending agent and a thickening agent.

15. (Original) A formulation according to claim 14, wherein said preservative is selected from edetic acid and its alkali salts, lower alkyl p-hydroxybenzoates, chlorhexidine, phenyl mercury borate, or benzoic acid or a salt, a quaternary ammonium compound, or sorbic acid or a salt thereof.

16. (Previously Presented) A formulation according to claim 14, wherein the suspending agent or thickening agent is selected from cellulose derivatives, gelatin, polyvinylpyrrolidone, tragacanth, ethoxose (water soluble binding and thickening agents on the basis of ethyl cellulose), alginic acid, polyvinyl alcohol, polyacrylic acid, or pectin.

17. (Previously Presented) A formulation according to claim 14, wherein the buffer comprises a citric acid-citrate buffer.

18. (Currently Amended) A formulation according to claim 14, wherein the buffer maintains the pH of the aqueous phase at from 3 to 7~~, preferably 4.5 to about 6.5~~.

19. (Previously Presented) A formulation according to claim 1, which is an aqueous suspension or solution.

20. (Previously Presented) A formulation according to claim 1, which is in the form of an aerosol, an ointment, eye drops, nasal drops, a nasal spray, an inhalation solution and other forms suitable for nasal or ocular administration.

21. (Original) A formulation according to claim 20, which is in the form of nasal drops or nasal spray.

22. (Original) A formulation according to claim 20, which is in the form of an aerosol.

23-24. (Canceled)

25. (Previously Presented) A formulation according to claim 1, which is in the form of an insufflation powder.

26. (Currently Amended) A pharmaceutical product ~~according to claim 1~~, comprising (i) azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, provided in an aerosol formulation preferably together with a propellant typically suitable for MDI delivery, and (ii) fluticasone or a pharmaceutically acceptable ester thereof~~at least one steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative~~

~~thereof~~, provided in an aerosol formulation preferably together with a propellant typically suitable for MDI delivery, as a combined preparation for simultaneous, separate or sequential use in the treatment of conditions for which administration of one or more anti-histamine and/or one or more steroid is indicated.

27. (Previously Presented) An aerosol formulation preferably suitable for MDI delivery comprising the formulation of claim 1, together with a propellant.

28. (Currently Amended) A pharmaceutical product comprising (i) azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, provided as an insufflation powder, and (ii) fluticasone or a pharmaceutically acceptable ester thereof~~at least one steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof~~, provided as an insufflation powder, as a combined preparation for simultaneous, separate or sequential use in the treatment of conditions for which administration of one or more anti-histamine and/or one or more steroid is indicated.

29. (Currently Amended) An insufflation powder formulation comprising (i) azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, and (ii) fluticasone or a pharmaceutically acceptable ester thereof~~at least one steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof~~, together with a pharmaceutically acceptable carrier or excipient therefor.

30. (Currently Amended) A pharmaceutical product comprising the formulation according to claim 1, wherein (i) azelastine, or a pharmaceutically acceptable salt thereof, and (ii) ~~wherein at least one steroid is selected from the group consisting of beclomethasone,~~ fluticasone~~, mometasone and~~ or a pharmaceutically acceptable esters thereof, as a combined preparation with said azelastine for simultaneous, separate or sequential use in the treatment of conditions for which administration of one or more anti-histamine and/or one or more steroid is indicated.

31-34. (Canceled)

35. (Currently Amended) A pharmaceutical product comprising the pharmaceutical formulation of claim 1, wherein said azelastine is azelastine hydrochloride and said pharmaceutically acceptable ester~~steroid~~ is fluticasone propionate, as a combined preparation for simultaneous, separate or sequential use in the treatment of conditions for which administration of one or more anti-histamine and/or one or more steroid is indicated.

36. (Currently Amended) A pharmaceutical formulation according to claim 1, wherein said azelastine is azelastine hydrochloride and said pharmaceutically acceptable ester~~steroid~~ is fluticasone propionate, together with a pharmaceutically acceptable carrier or excipient therefor.

37. (Currently Amended) A pharmaceutical product comprising the pharmaceutical formulation of claim 1, wherein said azelastine is azelastine hydrochloride and said pharmaceutically acceptable ester~~steroid~~ is fluticasone valerate, as a combined preparation for

simultaneous, separate or sequential use in the treatment of conditions for which administration of one or more anti-histamine and/or one or more steroid is indicated.

38. (Currently Amended) A pharmaceutical formulation according to claim 1, wherein said azelastine is azelastine hydrochloride and said pharmaceutically acceptable ester~~steroid~~ is fluticasone valerate, together with a pharmaceutically acceptable carrier or excipient therefor.

39-43. (Canceled)

44. (Currently Amended) A process of preparing a pharmaceutical product according to claim 26, which process comprises providing (i) azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, and (ii) fluticasone or a pharmaceutically acceptable ester thereof~~at least one steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof~~, as a combined preparation for simultaneous, separate or sequential use in the treatment of conditions for which administration of one or more antihistamine and/or one or more steroid is indicated.

45. (Currently Amended) A process of preparing a pharmaceutical formulation according to claim 1, which process comprises admixing a pharmaceutically acceptable carrier or excipient with azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, and fluticasone or a pharmaceutically acceptable ester thereof~~at least one steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof~~.

46-52. (Canceled)

53. (New) A formulation according to claim 1, wherein the pharmaceutically acceptable ester is fluticasone propionate.

54. (New) A formulation according to claim 1, wherein the pharmaceutically acceptable ester is fluticasone valerate.

55. (New) A pharmaceutical product comprising (i) azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, provided as a nasal spray, and (ii) fluticasone or a pharmaceutically acceptable ester thereof, provided as a nasal spray, as a combined preparation for simultaneous, separate or sequential use in the treatment of conditions for which administration of one or more anti-histamine and/or one or more steroid is indicated.

56. (New) A nasal spray formulation comprising (i) azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, and (ii) fluticasone or a pharmaceutically acceptable ester thereof, together with a pharmaceutically acceptable carrier or excipient therefor.

REMARKS/ARGUMENTS

Status of Claims

Claims 1, 4, 6, 7, 8, 18, 26, 28, 29, 30, 35, 36, 37, 38, 44, and 45 have been amended.

Claims 3, 5, 23-24, 31-34, 39-43, and 46-52 have been canceled.

New claims 53-56 have been added.

Thus, claims 1, 2, 4, 6-22, 25-30, 35-38, 44-45, and 53-56 are currently pending in this application.

Applicants hereby request further examination and reconsideration of the presently claimed application.

Restriction Requirement

Applicants affirm the election of group I, claims 1-22, 25-42 and 44-45. Furthermore, Applicants have amended the pending claims to recite the elected species, namely a pharmaceutical formulation comprising azelastine and fluticasone.

New Claims

Applicants have added new claims 53-54 directed to specific combinations of azelastine and specific pharmaceutically acceptable esters of fluticasone, which are supported by paragraph 0045 of the published application. Further, Applicants have added new claims 55-56, which mirror existing claims 28 and 29, and are drawn to a nasal spray as disclosed by paragraph 0010 of the published application. The new claims are patentable for the reasons set forth below.

Claim Rejections – 35 U.S.C. § 112

Claims 6 and 18 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants have amended claim 6 to remove the term "about." Applicants have also

amended claim 18 to remove the recitation of a narrower range of values. In consideration of the foregoing, Applicants respectfully request withdrawal of the rejections.

Claim Rejections – 35 U.S.C. § 102

Claims 1, 2, 4, 7, 9-10, 12-21, 30-31, and 44-45 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Cramer, European Patent No. 0780127 (hereinafter "*Cramer*"). Applicants note that claim 5 was not rejected as being anticipated by *Cramer*. Applicants have amended claim 1 to incorporate the limitations of now canceled claim 5 and respectfully submit that claims 1, 2, 4, 7, 9-10, 12-21, 30-31, and 44-45 are not anticipated by *Cramer*.

Claim Rejections – 35 U.S.C. § 103

Claims 1, 2, and 6 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Malmqvist-Granlund, et al., U.S. Patent No. 6,391,340 (hereinafter "*Malmqvist-Granlund*"). Applicants note that claim 5 was not rejected as being obvious in view of *Malmqvist-Granlund.* Applicants have amended claim 1 to incorporate the limitations of now canceled claim 5 and respectfully submit that claims 1, 2 and 6 are not obvious over *Malmqvist-Granlund.*

Claims 5 and 35-38 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over *Cramer*. Claims 22 and 26-27 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over *Cramer* in view of Modi, U.S. Patent No. 6,294,153 (hereinafter "*Modi*"). Claims 28-29 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over *Cramer* in view of Alfonso, et al., U.S. Patent No. 6,017,963 (hereinafter "*Alfonso*"). Accordingly, the pending claims stand or fall on the above-recited application of the primary reference, *Cramer*, alone or in combination with the secondary references, *Modi* or *Alfonso*, to independent claims 1, 26, 28, and 29. Applicants respectfully submit the pending claims are patentable because the broad genus disclosed in the primary reference does not render obvious the Applicants' claimed species directed to a

pharmaceutical formulation comprising azelastine and fluticasone. Further, Applicants submit herewith objective evidence of nonobviousness in that the claimed species directed to a pharmaceutical formulation comprising azelastine and fluticasone displays unexpectedly beneficial properties, is commercially successful, and fills a long felt but unsolved need.

The Legal Standard for Obviousness

The MPEP provides that "establishing a *prima facie* case of obviousness" requires, "the clear articulation of the reason(s) why the claimed invention would have been obvious." *See* MPEP § 2142. The MPEP also acknowledges that "[t]he Supreme Court in *KSR* noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit." *See* MPEP § 2143.

Moreover, in *KSR Int'l Co. v. Teleflex, Inc.*, the United States Supreme Court explained that, "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art," but, additionally whether "the claim extends to what is obvious." *See KSR Int'l Co. v. Teleflex, Inc.*, 82 USPQ2d 1385, 1397 (2007). Expounding on its edict, the Supreme Court went on to opine that an obviousness determination is based upon a "proper application of *Graham*," including consideration of "secondary factors" that may weigh against an obviousness determination. *See KSR Int'l Co. v. Teleflex, Inc.*, 82 USPQ2d at 1399 (citing *Graham v. John Deere Co. of Kansas City, et al.*, 383 U.S. 1, 148 USPQ 459 (1966)). The Office Action states:

> [t]he factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:
>
> 1. Determining the scope and contents of the prior art.
> 2. Ascertaining the differences between the prior art and the claims at issue.
> 3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

See Office Action at 10. In an attempt to satisfy the factual inquiries set forth in *Graham*, the Office Action addresses the "determining the scope and contents of the prior art" and "ascertaining the differences between the prior art and the claims at issue" portions of the *Graham* factual inquiries. However, the Office Action is silent with regards to the "resolving the level of ordinary skill in the pertinent art" and "considering objective evidence present in the application indicating obviousness or nonobviousness" portions of the *Graham* factual inquiries.

A. *Cramer* does not fairly suggest the elected species

In ascertaining the difference in the prior art and claim 5, the Office Action acknowledges "Cramer does not exemplify a composition comprising azelastine and fluticasone." *See* Office Action at 12. As such, the Office Action retreats to a "rationale-based" obviousness rejection based on the conclusion that:

> one of ordinary skill in the art would have been motivated to make a composition comprising azelastine and fluticasone because Cramer suggests that the combination of a gluccocortoid (i.e. fluticasone) and antihistamine (i.e. azelastine) provide improved relief of symptoms associated with seasonal or perennial allergic rhinoconjunctivitis.

See Office Action at 12.

The Office Action then supports its "rationale-based" rejection by stating, "the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made **because the prior art is fairly suggestive of the claimed invention**." *See* Office Action at 13 (emphasis added). As noted previously, "establishing a *prima facie* case of obviousness" requires, "the clear articulation of the reason(s) why the claimed invention would have been obvious." *See* MPEP § 2142. The Office Action's conclusion does not support a *prima*

facie case of obviousness because the Office Action does not clearly articulate why the claimed invention would be obvious.

The Office Action's reliance and discussion of *Cramer* does not articulate why the claimed pharmaceutical formulation comprising azelastine and fluticasone would be obvious in view of *Cramer's* general disclosure that mixtures of glucocorticoids and mixtures of antihstamines could be combined. The total number of **possible glucocorticoids specified in *Cramer* is six** (*beclomethasone, flunisolide, triamcinolone, fluticasone, mometasone and budesonide*) and the **total number of antihistamines is three** (*cetirizine, loratadine, azelastine*). Accoringly, there is a total of eighteen different combinations disclosed in *Cramer*. The present application claims just one of these combinations, and it is common ground that this particular combination (fluticasone and azelastine) is not explicitly mentioned in *Cramer*. The number of possible combinations rises exponentially when considering the breadth of the disclosed combinations of racemates, salts, and mixtures of the glucocorticoid and antihistamine agents.

As such, *Cramer*'s disclosure cannot be "fairly suggestive of the claimed invention," *see* Office Action at 13, because, as the MPEP states, the rationale for supporting an obviousness determination requires, "choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success." *See* MPEP § 2143; *see also KSR Int'l Co. v. Teleflex, Inc.*, 82 USPQ2d at 1397 (a combination of elements is obvious if "there are finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue."). Clearly, *Cramer*'s recitation of the possibility of innumerous combinations of compounds does not disclose a "finite number of identified, predictable solutions." *See id.*

Based on the foregoing, Applicants respectfully submit that the Office Action does not present a *prima facie* case of obviousness with regard to the instant claims.

B. Secondary considerations indicate that the combination of azelastine and fluticasone is nonobviousness

Assuming, without conceding, that the Office Action's "rationale and motivation" discussion is sufficient, nevertheless, the Office Action's suggestion of a *prima facie* case of obviousness must fail because the unaddressed "secondary considerations" described below render the instant claims nonobvious. *See KSR Int'l Co. v. Teleflex, Inc.*, 82 USPQ2d at 1399. Applicants provide herewith a Rule 1.132 declaration of inventor Geena Malhotra and the accompanying Exhibits A-C setting forth evidence of the following secondary considerations of nonobviousness.

1. The combination of azelastine and fluticasone displays unexpected, beneficial results

A showing of unexpected results may rebut a *prima facie* case of obviousness, and is particularly applicable in the inherently unpredictable chemical arts where minor changes may yield substantially different results. *See e.g., In re Soni*, 34 USPQ2d 1684, 1687 (Fed. Cir. 1995). Exhibit A of the declaration demonstrates that the claimed pharmaceutical formulation comprising azelastine and fluticasone has unexpected and beneficial stability. As noted in paragraph 2 of the declaration:

> The results in Table II show that the individual active materials (e.g., azelastine.HCl, budesonide, and fluticasone propionate) have good stability, in that the impurity levels are fairly constant in all the tests. The results in Table II also show that the combination of azelastine and budesonide are relatively unstable, with varying, and high amounts of impurities developing during the tests. Surprisingly, the results for azelastine and fluticasone show good stability throughout the tests, as the amount of impurity remains constant and at a low level.

These tests demonstrate that there is a clear unexpected advantage in product stability in formulating azelastine with fluticasone rather than with other steroids such as budesonide.

Improved product stability is extremely important in pharmaceutical compositions as is understood by those skilled in the art.

Furthermore, Exhibits B1 and B3 of the declaration demonstrate that a pharmaceutical formulation comprising azelastine and fluticasone has unexpected and beneficial efficacy when administered to patients. Specifically, Exhibit B1 notes that the use of DUONASE (a commercial pharmaceutical formulation comprising azelastine and fluticasone) "is very effective when compared [to] the available other nasal sprays." Likewise, Exhibit B3 notes (with emphasis added):

> DUONASE Nasal Spray is very very effective in all types of allergic rhinitis. Especially in "Seasonal allergic rhinitis", Fluticasone alone or azelastine alone also has been tried. But single drug was not effective as compared with the combination of both i.e. "DUONASE Nasal Spray".

Likewise, the remainder of the doctor statements in Exhibit B extol the therapeutic benefits of the claimed pharmaceutical formulation comprising azelastine and fluticasone. Such recognition by skilled artisans of the merits of the invention is further evidence of nonobviousness. *See Akzo N.V. v. United States Int'l Trade Comm'n*, 1 USPQ2d 1241, 1247 (Fed. Cir. 1986). These doctor statements demonstrate a clear, unexpected advantage in treatment efficacy, namely that the combination of azelastine and fluticasone provides a synergistic benefit in efficacy over azelastine alone or fluticasone alone.

As set forth above, the declaration provides strong evidence that the claimed pharmaceutical formulation comprising azelastine and fluticasone has unexpected and beneficial stability, and that upon administration to a patient, unexpected and beneficial enhanced efficacy is observed. Accordingly, the claimed pharmaceutical formulation comprising azelastine and fluticasone is nonobvious in view of these unexpected results.

2. The combination of azelastine and fluticasone is commercially successful

Commercial success is a strong factor favoring nonobviousness. *See e.g., Akzo N.V.* at 1246. As noted in paragraph 3 of the declaration, a pharmaceutical formulation comprising azelastine and fluticasonse is commercially available where approved as DUONASE nasal spray. The doctor statements set forth in Exhibit B provide further evidence of the commercial success of DUONASE nasal spray. Furthermore, as noted in paragraph 5 of the declaration the present application claiming a pharmaceutical formulation comprising azelastine and fluticasonse is licensed to Meda Pharmaceuticals, which specializes in respiratory, allergy, and cough-cold products. Given its expertise and knowledge in the field of treatment, the willingness of Meda Pharmaceuticals to license the pending application is further evidence of the commercial success of the claimed pharmaceutical formulation comprising azelastine and fluticasone. Accordingly, the claimed pharmaceutical formulation comprising azelastine and fluticasone is nonobvious in view of its commercial success.

3. The combination of azelastine and fluticasone fills a long-felt need

As set forth in *Graham*, the existence of a long-felt and unsolved need in the art is further evidence of nonobviousness. Applicants note that *Cramer* was published on June 25, 1997, which was over 10 years ago. Nonetheless, as noted in paragraph 5 of the declaration, inventor Geena Malhotra is unaware of another commercially available pharmaceutical formulation comprising an antihistamine and a steroid. Likewise, the doctor statement of Exhibit B4 notes that:

> I have been using nasal sprays from the year 1993, ever since I joined my present institution. I have used Beclomethasone, Budesonide, Azelastine, Fluticasone, Mometasone, with oral antihistamines down the line till date.
>
> The present combination spray of a weak (non sedating component) Azelastine and fluticasone (steroid component) is complete by itself in my patients of chronic simple rhinitis following nasal + sinus polyposis surgery and those unwilling for surgery or unfit for surgery.

Such "[f]irsthand practical knowledge of unsolved needs in the art, by an expert, is evidence of the state of the art." *See In re Piasecki*, 223 USPQ 785, 789 (Fed. Cir. 1984). Applicants respectfully submit that the evidence establishes a long-felt need dating back to 1993 that continued unsolved even after the subsequent publication of *Cramer* in 1997. Applicants further submit that the lack of another commercially available pharmaceutical formulation comprising an antihistamine and a steroid further evidences a long-felt need and the failure of others to address the need prior to the present invention. Accordingly, the claimed pharmaceutical formulation comprising azelastine and fluticasone is nonobvious given that it meets the long-felt need outlined above.

4. The secondary considerations require a finding of nonobviousness

As set forth above, the claimed pharmaceutical formulation comprising azelastine and fluticasone displays unexpected, beneficial results; is commercially successful; and fills a long-felt need in the art. Accordingly, the totality of the secondary considerations requires a finding that the pending claims are not obvious, and therefore patentable, in view of the prior art of record.

CONCLUSION

Consideration of the foregoing amendments and remarks, reconsideration of the application, and withdrawal of the rejections are respectfully requested by Applicants. No new matter is introduced by way of the amendment. It is believed that each ground of rejection raised in the Office Action dated January 23, 2009 has been fully addressed. If any fee is due as a result of the filing of this paper, please appropriately charge such fee to Deposit Account Number 50-1515 of Conley Rose, P.C., Texas. If a petition for extension of time is necessary in order for this paper to be deemed timely filed, please consider this a petition therefore.

If a telephone conference would facilitate the resolution of any issue or expedite the prosecution of the application, the Examiner is invited to telephone the undersigned at the telephone number given below.

Respectfully submitted,
CONLEY ROSE, P.C.

Date: 7-23-09

Rodney B. Carroll
Reg. No. 39,624

ATTORNEY FOR APPLICANTS

5601 Granite Parkway, Suite 750
Plano, Texas 75024
(972) 731-2288 (Telephone)
(972) 731-2289 (Facsimile)

PTO/SB/08a (06-09)
Approved for use through 07/31/2009. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	10518016
Filing Date	2005-07-06
First Named Inventor	Amar Lulla
Art Unit	1616
Examiner Name	Kristie Latrice Brooks
Attorney Docket Number	PAC/20632 US (4137-04700)

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	6787532	B2	2004-09-07	Biggadike, et al.	

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

U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20040242638	A1	2004-12-02	Yanni, et al.	
	2	20050192261	A1	2005-09-01	Jost-Price, et al.	
	3	20060228306	A1	2006-10-12	Lane	

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

FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] ¡	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	1519731	EP	B1	2009-04-15	Cipla, Ltd.		☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	10518016
	Filing Date	2005-07-06
	First Named Inventor	Amar Lulla
	Art Unit	1616
	Examiner Name	Kristie Latrice Brooks
	Attorney Docket Number	PAC/20632 US (4137-04700)

	2	2072051	EP	A1	2009-06-24	Cipla, Ltd.		☐
	3	2389530	GB	A	2003-12-17	Cipla, Ltd.		☐
	4	2003105856	WO	A1	2003-12-24	Cipla Limited		☐

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

NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	Foreign communication from the priority application - International Search Report, PCT/GB03/02557, September 17, 2003, 3 pages.	☐
	2	Foreign communication from the priority application - International Preliminary Examination Report, PCT/GB03/02557, August 26, 2004, 6 pages.	☐
	3	Foreign communication from a related counterpart application - Examination Report, EP Application 03738280.1, November 10, 2005, 4 pages.	☐
	4	Foreign communication from a related counterpart application - Examination Report, EP Application 03738280.1, July 18, 2007, 5 pages.	☐
	5	Applicants response to foreign communication - EP 03738280.1, May 22, 2006, 36 pages.	☐
	6	Applicants response to foreign communication - EP 03738280.1, January 18, 2008, 17 pages.	☐

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	10518016
	Filing Date	2005-07-06
	First Named Inventor	Amar Lulla
	Art Unit	1616
	Examiner Name	Kristie Latrice Brooks
	Attorney Docket Number	PAC/20632 US (4137-04700)

EXAMINER SIGNATURE			
Examiner Signature		Date Considered	

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

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	10518016
	Filing Date	2005-07-06
	First Named Inventor	Amar Lulla
	Art Unit	1616
	Examiner Name	Kristie Latrice Brooks
	Attorney Docket Number	PAC/20632 US (4137-04700)

CERTIFICATION STATEMENT

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

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

OR

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

☐ See attached certification statement.

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

☐ None

SIGNATURE

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

Signature	/Rodney B. Carroll/	Date (YYYY-MM-DD)	2009-07-23
Name/Print	Rodney B. Carroll	Registration Number	39624

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

Privacy Act Statement

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

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

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

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

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

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

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

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

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

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

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

INTERNATIONAL SEARCH REPORT

Internal application No
PCT/GB 03/02557

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/55 A61K31/56 A61K31/57 A61K31/58 A61K9/00
A61P37/08 A61P27/14 A61P11/06 //(A61K31/56,31:55),
(A61K31/57,31:55),(A61K31/58,31:55)
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 A61P

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)
EPO-Internal, MEDLINE, WPI Data, PAJ, BIOSIS, EMBASE, 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	WO 97 01337 A (MCNEIL PPC INC) 16 January 1997 (1997-01-16) page 2, line 8 -page 8, line 25 ---	1-50
X	EP 0 780 127 A (PROCTER & GAMBLE) 25 June 1997 (1997-06-25) page 2, line 34 -page 5, line 30; example 3 --- -/--	1-50

[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
1 September 2003	17/09/2003

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	Vandenbogaerde, A

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

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE MEDLINE 'Online! US NATIONAL LIBRARY OF MEDICINE (NLM), BETHESDA, MD, US; 2000 PORTMANN D ET AL: "'Acceptability of local treatment of allergic rhinitis with a combination of a corticoid (beclomethasone) and an antihistaminic (azelastine)!" Database accession no. NLM11233712 XP002252974 abstract & REVUE DE LARYNGOLOGIE - OTOLOGIE - RHINOLOGIE. FRANCE 2000, vol. 121, no. 4, 2000, pages 273-279, ISSN: 0035-1334 ---	1-50
X	BUSSE W W ET AL: "CORTICOSTEROID-SPARING EFFECT OF AZELASTINE IN THE MANAGEMENT OF BRONCHIAL ASTHMA" AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE, AMERICAN LUNG ASSOCIATION, NEW YORK, NY, US, vol. 153, no. 1, 1996, pages 122-127, XP000604179 ISSN: 1073-449X page 127, column 1, paragraph 2 -----	1-50

INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/GB 03/02557

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9701337 A	16-01-1997	AU 6392496 A	30-01-1997
		WO 9701337 A1	16-01-1997
EP 0780127 A	25-06-1997	EP 0780127 A1	25-06-1997

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference CPW/20632	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/GB 03/02557	International filing date *(day/month/year)* 13.06.2003	Priority date *(day/month/year)* 14.06.2002
International Patent Classification (IPC) or both national classification and IPC A61K31/55		
Applicant CIPLA LIMITED 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 6 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 consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - 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 Rule 66.2(a)(ii) 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
07.01.2004	26.08.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Vandenbogaerde, A Telephone No. +49 89 2399-7874

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB 03/02557

I. Basis of the 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

1-16 as originally filed

Claims, Numbers

1-50 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. 46-47,49-50 with respect to industrial applicability

   because:

   ☒ the said international application, or the said claims Nos. 46-47,49-50 with respect to industrial applicability 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	/
	No:	Claims	1-50
Inventive step (IS)	Yes:	Claims	/
	No:	Claims	1-50
Industrial applicability (IA)	Yes:	Claims	1-45, 48: YES / 46-47,49-50: see separate sheet
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 46-47 and 49-50 relate 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).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO 97 01337 A (MCNEIL PPC INC) 16 January 1997 (1997-01-16)

D2: EP-A-0 780 127 (PROCTER & GAMBLE) 25 June 1997 (1997-06-25)

D3: DATABASE MEDLINE [Online] US NATIONAL LIBRARY OF MEDICINE (NLM), BETHESDA, MD, US; 2000 PORTMANN D ET AL: '[Acceptability of local treatment of allergic rhinitis with a combination of a corticoid (beclomethasone) and an antihistaminic (azelastine)]' Database accession no. NLM11233712 XP002252974 & REVUE DE LARYNGOLOGIE - OTOLOGIE - RHINOLOGIE. FRANCE 2000, vol. 121, no. 4, 2000, pages 273-279, ISSN: 0035-1334

D4: BUSSE W W ET AL: 'CORTICOSTEROID-SPARING EFFECT OF AZELASTINE IN THE MANAGEMENT OF BRONCHIAL ASTHMA' AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE, AMERICAN LUNG ASSOCIATION, NEW YORK, NY, US, vol. 153, no. 1, 1996, pages 122-127, XP000604179

- D1 discloses (cf. page 2 line 8 - page 8 line 25) a combination of (i) a topical nasal antihistaminic, i.e. levocabastine, azelastine or azatadine, and (ii) a topical nasal steroid, i.e. beclomethasone, flunisolide, triamcinolone, dexamethasone or budesonide, as nasal spray or nasal drops for the treatment of allergic rhinitis.
- D2 describes (cf. page 2 line 34 - page 5 line 30, example 3) a combination of (i) an antihistamine possessing leukotriene inhibiting properties, i.e. cetirizine, loratadine or azelastine, and (ii) a glucocorticoid, i.e. beclomethasone, flunisolide, triamcinolone, fluticasone, mometasone or budesonide, as nasal

spray for the treatment of allergic rhinoconjunctivitis.

- D3 discloses (cf. abstract) a combination of (i) the antihistamine azelastine and (ii) the corticoid beclomethasone as nasal spray for the local treatment of seasonal or aperiodic rhinitis.
- D4 describes (page 126-127, discussion) that the combined use of (i) azelastine and (ii) corticosteroid medication in patients with asthma allowed patients to achieve a reduction in the use of inhaled corticosteroids while showing improvements in the severity of asthma symptoms and in pulmonary function.

V.1 Claims 1-43 - *Composition (for use in medicine)*: Novelty - Inventive step

V.1.1 The subject-matter of claims 1-43 relates to a composition per se or to a composition for use in medicine comprising (i) azelastine and (ii) a steroid, i.e. beclomethasone, mometasone, fluticasone, budesonide or cyclosenide.

V.1.2 The subject-matter of independent claim 1 is not novel according to Article 33(2) PCT over the teaching of D1, D2, D3 or D4.

V.1.3 Dependent claims 2-22 and 25 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step, the reasons being as follows: Document D1, which is considered to represent the most relevant state of the art, discloses (cf. page 2 line 8 - page 8 line 25) a combination of (i) a topical nasal antihistaminic, i.e. levocabastine, azelastine or azatadine, and (ii) a topical nasal steroid, i.e. beclomethasone, flunisolide, triamcinolone, dexamethasone or budesonide, as nasal spray or nasal drops for the treatment of allergic rhinitis. The problem to be solved by the present invention may therefore be regarded as the provision of alternative formulation comprising (i) azelastine and (ii) a steroid for the treatment of allergic disorders of eye and nose or airway disorders. It would be obvious to use an alternative steroid, to use alternative carriers or to prepare an alternative formulation (i.e. inhalation formulation), because no unexpected technical effect can be seen.

V.1.4 The same objections also apply to independent claims 23 (and dependent claims 24-25), 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42 and 44.

V.2 Claims 46-50 - *Therapeutical application*: Novelty - Inventive step

V.2.1 The subject-matter of claims relates to the therapeutical application of a composition comprising (i) azelastine and (ii) a steroid, i.e. beclomethasone,

mometasone, fluticasone, budesonide or cyclosenide for the treatment of conditions for which administration of one or more anti-histamine and/or one or more steroid is indicated, i.e. irritation or disorders of the nose or eye (e.g. allergic rhinitis, rhinoconjunctivis), or airway disorders (e.g. asthma).

V.2.2 The subject-matter of claims 46-50 is not novel according to Article 33(2) PCT and/or cannot be considered as involving an inventive step in the sense of Article 33(3) PCT for the same reasons as given under point V.1.

V.3 Claims 44-45 - *Process*: Novelty - Inventive step

V.3.1 The subject-matter of claims 44-45 relates to a process for preparing a pharmaceutical composition comprising (i) azelastine and (ii) a steroid, i.e. beclomethasone, mometasone, fluticasone, budesonide or cyclosenide.

V.3.2 The subject-matter of claims 46-50 is not novel according to Article 33(2) PCT and/or cannot be considered as involving an inventive step in the sense of Article 33(3) PCT, since merely standard processes are used for preparing a composition which is already known (cf. point V.1).

V.4 Industrial applicability

For the assessment of the present claims 46-47 and 49-50 on the question whether they are 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.

Electronic Patent Application Fee Transmittal

Application Number:	10518016
Filing Date:	06-Jul-2005
Title of Invention:	Combination of azelastine and steroids
First Named Inventor/Applicant Name:	Amar Lulla
Filer:	Rodney B. Carroll/Linda Kerrick
Attorney Docket Number:	PAC/20632 US (4137-04700)

Filed as Large Entity

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

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Independent claims in excess of 3	1614	3	220	660
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension - 3 months with $0 paid	1253	1	1110	1110
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**1950**

Electronic Acknowledgement Receipt

EFS ID:	5758556
Application Number:	10518016
International Application Number:	
Confirmation Number:	4912
Title of Invention:	Combination of azelastine and steroids
First Named Inventor/Applicant Name:	Amar Lulla
Customer Number:	30652
Filer:	Rodney B. Carroll/Edith Shek
Filer Authorized By:	Rodney B. Carroll
Attorney Docket Number:	PAC/20632 US (4137-04700)
Receipt Date:	23-JUL-2009
Filing Date:	06-JUL-2005
Time Stamp:	17:44:41
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$1950
RAM confirmation Number	3956
Deposit Account	501515
Authorized User	

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

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		072309ResponsetoOfficeAction.pdf	722034 54b255c93b7e86a35bf11a997bb3f2d5817bdce0	yes	19
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Amendment/Req. Reconsideration-After Non-Final Reject		1	1	
	Claims		2	9	
	Applicant Arguments/Remarks Made in an Amendment		10	19	
Warnings:					
Information:					
2	Rule 130, 131 or 132 Affidavits	072309Rule132Declaration.pdf	4060423 4fe2f070d92ece9c5b819fa9560baf447a01faba	no	23
Warnings:					
Information:					
3	Information Disclosure Statement (IDS) Filed (SB/08)	072309_IDSForm.pdf	853302 8157fe30e02d5dfa722ef20954815d7ce89fddcd	no	5
Warnings:					
Information:					
4	Foreign Reference	EP1519731B1.pdf	121829 cc89b536942ae0a658d56b56fc2167a5466c2ae0	no	14
Warnings:					
Information:					
5	Foreign Reference	EP2072051.pdf	179482 cddc3f3b252230a76bb90671f70ce6f5d03b9e9d	no	16
Warnings:					
Information:					
6	Foreign Reference	GB2389530.pdf	489847 f34067d2dfc2319c1ef547650748b7bd3bce8da0	no	12
Warnings:					
Information:					
7	Foreign Reference	WO2003105856A1.pdf	1321234 17ae59b3f05953a5c1ed3aaaeedb4febc07e4362	no	27

Warnings:					
Information:					
8	NPL Documents	091703_ISR_PCTGB0302557.pdf	94075 21d53a6b7cce6ff46089fbaab00e1b52278dd21f	no	3
Warnings:					
Information:					
9	NPL Documents	082604_IPER_PCTGB0302557.pdf	312809 45a2ada841debd974410c85c58dddfcb35ab6aa5	no	6
Warnings:					
Information:					
10	NPL Documents	111005_ExamReport_GB.pdf	157090 472568692a1d980cf51c00aae23f0a04331e71d0	no	4
Warnings:					
Information:					
11	NPL Documents	071807_ExamReport_GB.pdf	211885 1d1aaf32e179ae33441aa46117f50a440400ec19	no	5
Warnings:					
Information:					
12	NPL Documents	052206_ResponsetoExamReport.pdf	1489368 feabaa99d5fc1deeee6d0639c920e2783b7e46b9	no	36
Warnings:					
Information:					
13	NPL Documents	011809_ResponsetoExamReport.pdf	590666 123bf484da544223a8780aa7e6ec3ce2eb956e6b	no	14
Warnings:					
Information:					
14	Fee Worksheet (PTO-875)	fee-info.pdf	33815 0f522b502297a5236e946caf45030ad0b670b2a4	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	10637859	

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Amar Lulla, *et al.*	§	
		§	Group Art Unit: 1616
Serial No.:	10/518,016	§	
		§	Examiner: Kristie Latrice Brooks
Filed:	July 6, 2005	§	
		§	Confirmation No.: 4912
For:	COMBINATION OF AZELASTINE AND STEROIDS	§	
		§	

DECLARATION UNDER 37 CFR § 1.132

I, Geena Malhotra, hereby declare and say that:

1. I am a co-inventor of the invention claimed in the above-identified patent application.

2. Attached as Exhibit A is comparison data for five compositions:

   Column 1: Azelastine.HCl
   Column 2: Budesonide
   Column 3: Azelastine.HCl & Budesonide
   Column 4: Fluticasone Propionate
   Column 5: Azelastine.HCl and Fluticasone Propionate

Table I of Exhibit A sets for the ingredient list for the five compositions. Table II of Exhibit A sets forth comparative stability data for the five compositions. The results in Table II show the impurity levels in the initial compositions, and after storage under certain conditions: for example "25/60 RH at 1 M" means the composition was stored for one month at a temperature of 25 degrees C and at a relative humidity of 60. The results in Table II show that the individual active materials (e.g., azelastine.HCl, budesonide, and fluticasone

propionate) have good stability, in that the impurity levels are fairly constant in all the tests. The results in Table II also show that the combination of azelastine and budesonide are relatively unstable, with varying, and high amounts of impurities developing during the tests. Surprisingly, the results for azelastine and fluticasone show good stability throughout the tests, as the amount of impurity remains constant and at a low level.

3. Attached as Exhibit B is a compilation of statements from 6 medical practitioners, labeled B1-B6, along with typed transcriptions. As is self-evident, these statements attest to various advantages and superior results associated with patient use of the DUONASE product comprising azelastine and fluticasone.

4. A pharmaceutical formulation comprising azelastine and fluticasonse is commercially available where approved as DUONASE nasal spray, as shown in attached Exhibit C containing information from the following website: http://www.cipladoc.com/therapeutic/admin.php?mode=prod&action=disp&id=213.

5. I am unaware of another commercially available pharmaceutical formulation comprising an antihistamine and a steroid.

6. The present application is licensed to Meda Pharmaceuticals.

7. I, Geena Malhotra, further 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 are made with the knowledge that willful false statements and the like so made are punishable by fine, 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 this application or any patent issuing thereon.

Date: 3rd July 2009.

Gmalhotra

Name: GEENA MALHOTRA

Exhibit A, Table I: Comparative Composition data of Azelastine with steroids

Ingredients →	Azelastin (%w/w)	Budesonide (%w/w)	Azelastine+Budesonide (%w/w)	Fluticasone (%w/w)	Aze+Flu (%w/w)
Drugs	137 mcg	64 mcg	137+64 mcg	50 mcg	140+50 mcg
MCC+CMC (Avicel RC)	-	-	2.0	0.75	2.0
HPMC	0.10	-	-	-	-
Dispersible cellulose	-	1.25	-	-	-
Dextrose Anhy.	-	-	-	2.5	-
Anhy. Glucose	-	5.0	-	-	-
Glycerin	-	-	2.3		2.3
Polysorbate 80		0.016	0.005	0.0025	0.005
BKC 10% w/v solution	0.125	-	0.005	100 ml	0.10
Phenyl ethyl alcohol	-	-	-	0.125	0.25
Pot sorbate	-	0.12	-	-	-
Disodium EDTA	0.05	0.01	0.01		0.01
Sodium Chloride	0.68				
Citrate Monohydrate	0.048	-	-	-	-
Disodium Phosphate	0.322	-	-	-	-
Hydrochloric acid		q.s.			

Exhibit A, Table II: Comparative Stability data of Azelastine with steroid Compositions

Stability tests →	**Azelastine**	**Budesonide**	**Azelastine + Budesonide**	**Fluticasone**	**Azelastine + Fluticasone**
	INITIAL	**INITIAL**	**INITIAL**	**INITIAL**	**INITIAL**
Assay	100	97.6	98+97	101.6	100+101.12
pH	6.78	4.51	6.0	6.4	6.1
Total Impurity	0.03	0.26	2.32+0.11	0.52	0.6
	25/60 RH at 1M	**25/60 RH at 1M**	**25/60 RH at 1M**	**25/60 RH at 1M**	**25/60 RH at 1M**
pH	6.86	4.68	5.94	Not Done	Not Done
Total Impurity	0.12	0.25	0.97 + 0.07	Not Done	Not Done
	25/60 RH at 3 M	**25/60 RH at 3 M**	**25/60 RH at 3 M**	**25/60 RH at 3 M**	**30/65 RH at 1M**
pH	6.76	4.6	5.96	6.21	5.85
Total Impurity	0.13	0.42	5.39+0.16	0.46	0.84
	40/75 RH at 1M	**40/75 RH at 1M**	**40/75 RH at 1M**	**40/75 RH at 1M**	**40/75 RH at 1M**
pH	6.86	4.69	5.92	6.35	5.82
Total Impurity	0.13	0.29	5.53+0.05	0.52	0.89
	40/75 RH at 3 M	**40/75 RH at 3 M**	**40/75 RH at 3 M**	**40/75 RH at 3 M**	**40/75 RH at 3 M**
pH	6.76	4.61	5.91	5.98	5.81
Total Impurity	0.18	0.49	18.29+0.23	0.53	0.85

Exhibit B1

Dr. C.M. Mathew Chooracken
B. Sc., M. B. B. S., M. S. (E. N. T.) D. L. O.
Senior Specialist in E.N.T.
Civil Surgeon
District Hospital, Kottayam
Reg. No. 9473

Consultation:
Behind Margin Free Market
Near Kottayam East Police Station
Collectorate P.O., Kottayam - 686 002
Ph: 2564884, Mb: 9447288822

To Cipla Respiratory L

I have been using the Duonase nasal spray regularly for my nasal allergy patients. I found it is very effective when compared to the available other nasal sprays. Oral medication can be avoided as well.

Kottayam
23/8/05

Dr. C. M. Mathew Chooracken
B. Sc., M. B. B. S., M.S. (E.N.T.) D. L. O.
Senior Specialist in E. N. T.
Civil Surgeon,
District Hospital, Kottayam
Reg. No. 9473

[redacted]

Dr. C.M.MATHEW CHOORACKEN

To Cipla Respiratory

I have been using the Duonase nasal spray regularly for my nasal allergic patients. I found it is very effective when compared the available other nasal sprays. Oral medication can be avoided as well.

Kottayam
23/8/05

Exhibit B2

Confidential

डॉ. पी.एन. तेजनकर
एम. एस. (ई.एन.टी.)
नाक, कान, गला एवं गर्दन रोग विशेषज्ञ
पूर्व रजिस्ट्रार ई.एन.टी. हॉस्पिटल, बाम्बे

क्लिनिक

गुजराती समाज, नई सड़क, उज्जैन
☎ 2561981
समय प्रातः 11 से 2.00

जय मेडिकल सेन्टर (वसावड़ा पेट्रोल पम्प के पा
घंटाघर, फ्रीगंज, उज्जैन ☎ 2514884
समय सायं 6 से 8.30

रविवार अवकाश

विशेषज्ञ

- नाक एवं सायनस इन्डोस्कोपी (दूरबीन द्वारा आपरेशन)
- माइक्रोलेरिन्जियल सर्जरी
- माइक्रोइयर सर्जरी (जर्मनी, फ्रांस एवं स्वीटजरलेण्ड से प्रशिक्षण प्राप्त)
- नाक की प्लास्टिक सर्जरी (राईनोप्लास्टी)

18.8.200

Regarding Drowness

Using this product for last so many days

This is ideal, first line agent for the patient. The combination is adequate to deal with all types of allergy. It

- Acts on both phases (early and late phase of allergy i.e. inhibits)
- Antagonise H1 receptor activity & few side effect.
- Acts on multiple symptoms

The systemic bio-availability is less so can be used for a longer period without side effect.

Tough to allergy Safe to H...

[signature]

DR.P.N.TEJANKAR

M.S. (E.N.T)
E.N.T and Neck Specialist
Ex-Registrar E.N.T. Hospital, Bombay

CLINIC

Gujrati Samaj,
Nai Sadak, Ujjain
☎ 2561981
Time Mor: 11 to 2.00
SUNDAY

Jai Medical Centre (Near
Vasavda petrol pump)
Ghantaghar, Freegunj, Ujjain
☎ 2514884
Time:eve. 6 to 8.30
HOLIDAY

Specialist

• Nose and sinus endoscopy • Microlaryngeal Surgery • Microear Surgery (Trained from Germany, France and Switzerland) •Plastic Surgery of the Nose (rhinoplasty)

Regarding Duonase

Using this product for last so many days. This is ideal, first line agent for the patient. The combination is adequate to deal with all type of allergy.

- Acts on both phases (early as well as late phase of allergy i.e. inhibit)

- Antagonises the H1 receptor activity with few side effect.

- Acts on multiple symptoms.

- The systemic bioavailability is less so can be used for a longer period without side effect.

Tough to allergy safe to Nose

Exhibit B3

Confidential

डॉ. प्रसाद ग. जवळेकर एम. एस. (ई. एन. टी.)

रजि. नं. ०७१८८२

कृष्णा जनरल हॉस्पिटल
गल्हार्स हॉस्पीटल, पी. सी. एम. टी. चौक, भोसरी,
पुणे ४११०३९. ☎ २७५२९५१६
वेळ : संध्या. ५ ०० ते ८-०० वा.

रविवार बंद

(कॉन्सल्टिंग-ईएनटी सर्जन)
धन्वंतरी कान, नाक, घसा हॉस्पि
ओंकार रोड, नाशिक
रा. जुन्नर, जि. पुणे, ४१०
☎ ०२५४२-(हॉस्पि.) २४४७६६, (नि.) २४३

Date. 27.8.05

I have prescribed "Buonase Nasal Spra for 258 patients Since Aug 2004 to Aug 2005. And I found that Buonase Nasal Spray very very effective in all types of allergi rhinitis. Especially in "seasonal allerg rhinitis." Fluticasone alone or azelast alone also has been tried. But sinc drug was not effective as compared with the combination of both i.e "Buonase Nasal Spray."

So I hereby strongly recommen Buonase Nasal Spray for allergic rhi

Chavdar

DR. PRASAD JAWALEKAR M.S (E.N.T)

Reg.no.071882
Krishna General Hospital
Gavhane building, P.C.M.T Chowk,
Bhosari,Pune 411039. ☎ 27129516
Time: eve. 5-00 to 8-00 SUNDAY CLOSED

E.N.T Specialist
Dhanvantari E.N.T.Hospital
Khodad Road, Narayangaon,
Taluka Junnar, Dist. Pune 410504
☎02132-(Hosp.)244766 (R)243969

I have prescribed "Duonase Nasal spray" for 258 patients since Aug 2004 to Aug 2005. And I found that Duonase Nasal Spray very very effective in all types of allergic rhinitis. Especially in "Seasonal allergic rhinitis", Fluticasone alone or azelastine alone also has been tried. But single drug was not effective as compared with the combination of both i.e. "Duonase Nasal Spray".

So I hereby strongly recommend Duonase Nasal Spray for allergic rhinitis.

Exhibit B4

No: 25469

Confidential

Dr. Manish Munjal

M.B.B.S., M.S. Diplomate of National Board (ENT), M.N.A.M.S.
D.H.A., D.N.D., D.N.A., D.T.M., D.M.S.

EAR – NOSE – THROAT AND HEAD NECK SURGEON

Ph.: 2300182
Mobile : 98551-23462
E-mail : mmunjal@glide.net.in

Consultant Otorhinolaryngology & Head-Neck Services
Dayanand Medical College & Hospital, Ludhiana
Formerly Consultant Christian Medical College
and Brown Hospital, Ludhiana.

Clinic-cum-Residence
52-C, Udham Singh Nagar,
Adj. P.A.U. Gate No.4,
Next to Lions Bhawan, Ludhiana

To

Sy.

As.

Pr.

Ro

Ln

I have been using nasal sprays from the year 1993, ever since I joined my present institution. I have used beclomethasone, budesonide, azelastine, fluticasone, mometasone, with oral antihistamines. Under Treatment of: Cross Consult.: down the line till date.

Rin.

The present combination spray of a weak (non-sedating component) azelastine and fluticasone (steroidal component) is comparable by itself in my patients of chronic simple rhinitis following nasal & sinus Polyposis surgery and nose correction surgery or septal surgery.

Wch.

There is a response noted with Rin a week in a few patients but the maximum

Opp.

Ill.

N. Singh

Consultations : Morning 8.30 A.M. to 1.00 P.M. 5.30 P.M. to 8.30 P.M.
Evening by appointment only Sunday : 10.30 to 1.00 P.M.

[redacted]

Confidential

number of patients responded very well after three weeks of therapy.

Recurrences of polyposis after functional endoscopic sinus surgery is markedly reduced. Eye itching, crusting and nasal bleeding noted with other preparations is not noted to that much extent

Of course caution/avoidance in diabetic and hypertensive patients is required for fear of worsening or inducing a fungal pathology (though have not found much literature on this issue on the net)

The combination therapy (Dymista) is gradually tapered off by me in two to three months time.

Occasionally usage is not advised the entire bottle must be finished for having the best of results.

Hoping the future is bright for the combination and no one digs up a bone. Contraindication or side effects

[redacted]

DR. MANISH MUNJAL

I have been using nasal sprays from the year 1993, ever since I joined my present institution. I have used Beclomethasone, Budesonide, Azelastine, Fluticasone, Mometasone, with oral antihistamines down the line till date.

The present combination spray of a weak (non sedating component) Azelastine and fluticasone (steroid component) is complete by itself in my patients of chronic simple rhinitis following nasal + sinus polyposis surgery and those unwilling for surgery or unfit for surgery.

There is a response noted within a week in a few patients but the maximum number of patients respond very well after three weeks of therapy.

Recurrences of polyposis after functional endoscopic sinus surgery is markedly reduced. Eye itching, crusting and nasal bleed as noted with earlier preparations is not noted to that much extent of course caution/avoidance in diabetic and hypertensive patients is required for fear of worsening or inducing and fungal pathology (though have not found much literature on the issue on the net).

The combination Therapy (DUONASE) is gradually tapered off by me in two to three months time.

Occasionally usage is not advised. The entire bottle must be finished for having the best of results.

Hoping the future is bright for this combination and no one digs up some contra indication or side effect of this indication.

Exhibit B5

VATS E.N.T. CENTRE

(दिल्ली सरकार द्वारा पंजीकृत)
698/5, Yamuna Vihar Road, (Road No. 66), Maujpur, Delhi-110053
Ph. : 229111
: 22918
: 22911

Dr. Suresh Vats
M.B.B.S., M.S. (ENT)
CONSULTANT EAR, NOSE & THROAT SURGEON
Formerly ENT Surgeon
ST. STEPHEN'S HOSPITAL
LNJP & GB PANT HOSPITAL

डॉ० सुरेश वत्स
एम.बी.बी.एस., एम.एस.(ई.एन.टी.)
कान, नाक व गला रोग विशेषज्ञ एवं सर्जन
समय : सुबह 10 से 1 तक शाम 5 से 8 तक
Reimbursible Yes/No. S. No. .... (रविवार अवकाश)

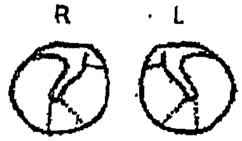
Name .... Age & Sex .... Resi. .... Date .... A

रविवार को केवल Audiometary एवं Speech Therapy
रवि. बुध. शुक्र सुबह 10 से 1 व मंगल शाम 7 से 8 बजे
P.T. Audiogram/Hearing Assessment
Aided Audiogram
Hearing Aid Trial
Speech Assessment
Speech Therapy
Caloric Test
Impedence

Hb TLC, DLC, B.T., C.T.
ESR, Mx-Test
Blood Sugar R-F-Pp., Blood Urea
Urine R/F & M/e
Prothrombin time Platelets Count
HBsAg, HIV 1 & II
AEC IgE, Nasal smear for Eosinophils
VDRL, ASLO Titre
T3 T4 TSH
Sputum smear for AFB
Throat/Nasal/Ear/Swab C & S
Blood - mix & cyst
FNAC

X-Ray Mastoids - Lat. Oblique(R) Towne
X-Ray PNS - Waters
X-Ray Naso-Pharynx-soft Tissue (Lateral)
X-Ray Neck soft Tissue - Lateral
X-Ray cervical Spine - Lat. & A.P.
X-Ray - Styloids Process (B-Lateral)
X-Ray Occlusal view for of mouth
X-Ray - Submandibular region - Lat. Rt. - Lt.
X-Ray - Internal Auditory Meatus
X-Ray T.M. Joint Lat. Open & closed Jaw
X-Ray - Nasal Bones - Lateral
X-Ray Skull - AP - Lateral
X-Ray - Chest P.A. View
Barium Swallow
C.T. Scan - PNS - Coronal 3 mm cuts
C.T. Scan - Temporal bones
C.T. Scan - Neck - Head
E.C.G.

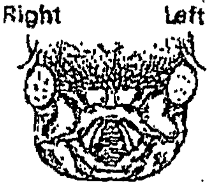
R L



Rinne's
Weber's

I/L Exa.:

Right Left



Durhase nasal spray
is unique & distinct fr
other available nasal spr
due to its combined anti
allergic & anti inflammatory
properties. It is an excel
product, effective in the
patients c Allergic
Rhinitis with or wit.
concomitant Bronchia

[illegible]

Allergy: Worth Trying / Agt to use in certain patients ... oral antihistamine may be harmy

17/8/08

Dr. SURESH VATS
M.S. (ENT)
Sr. CONSULTANT EAR, NOSE & THROAT SURGEON
Reg. No. MCI-2103, DMC-1712
698/5, Road No. 66, Manipur, Delhi-55

Dr. SURESH VATS

Duonase Nasal spray is unique & distinct from other available nasal sprays due to it combined Anti-allergic & anti-inflammatory properties. It is an excellent product, effective in majority of patients with allergic Rhinitis with or without concomitant Bronchial Allergy. Worth Trying. Safe to use in certain patients where oral antihistamine may be harmful.

Exhibit B6

डॉ. बी. बी. माथुर
एम.डी.

वरिष्ठ विशेषज्ञ एवं एसोसियट प्रोफेसर
चेस्ट एवं टी.बी. विभाग
सरदार पटेल मेडिकल कॉलेज, बीकानेर
RMC No. 7458

Dr. B. B. Mathur
M.D.

Senior Consultant & Associate Professor
Chest & T.B., Hospital
S.P. Medical College, BIKANER
✆ Hos. :0151-2226333,Res.0151-2528789

Ref No.

Date 17/8/05

Duonase Nasal Spray is highly effective in controlling symptoms and subsequent relapse in patients of Allergic Rhinitis. I have used this product in many patients and due to its efficacy it gives confidence to patients & it take care symptoms due to rapid onset of action and long lasting relief due to anti-inflammatory activity

डॉ. बी. बी. माथुर
एसोसियट प्रोफेसर
चे. बी. एंड चेस्ट विभाग
पटेल मेडिकल कॉलेज
बीकानेर (राज.)

निवास–III/7, मेडिकल कॉलेज कैम्पस, नागनेचीजी रोड, बीकानेर 334003 ✆ 0151-2528789
Resi. : III/7, Medical College Campus, Nagnechiji Road, Opposite Swimming Pool, BIKANER ✆ 0151-2528789

Dr. B.B. MATHUR

Duonase Nasal spray is highly effective in controlling symptoms and subsequent relapse in patients of Allergic Rhinitis. I have used this product in many patients and due to its efficacy it gives confidence to patients as it take care symptoms due to rapid onset of action and long lasting relief due to anti-inflamattory action.

Exhibit C

Cipla

Therapeutic Index

Nasal Preparations

Duonase Nasal Spray

Azelastine hydrochloride & Fluticasone propionate

Each spray delivers
Azelastine hydrochloride BP ..... 140 mcg
Fluticasone propionate BP ..... 50 mcg

Composition
Fluticasone propionate BP ..... 0.0357% w/v
Azelastine Hydrochloride BP ..... 0.10% w/v
Benzalkonium Chloride NF ..... 0.01% w/v
(as preservative)
Phenyl Ethyl alcohol USP ..... 025% v/v
(as preservative)

Description
Duonase is an antihistamine-corticosteroid combination available as a metered spray formulation for intranasal administration. It contains azelastine hydrochloride, which is a s generation H 1 receptor antagonist with potent topical activity and fluticasone propionate, synthetic corticosteroid with anti-inflammatory properties.

Pharmacology
As Duonase is a combination of Azelastine and Fluticasone; the pharmacological properti both the molecules are given separately.

Pharmacology of Azelastine Hydrochloride
Azelastine hydrochloride, a phthalazinone derivative, exhibits histamine H 1 -receptor ant activity in isolated tissues, animal models, and humans. The major metabolite, desmethylazelastine, also possesses H 1 -receptor antagonist activity.

Pharmacokinetics and Metabolism
After intranasal administration, the systemic bioavailability of azelastine hydrochloride is approximately 40%. Maximum plasma concentrations (Cmax) are achieved in 2-3 hours. I on intravenous and oral administration, the elimination half-life, steady-state volume of distribution, and plasma clearance are 22 hours, 14.5 L/kg, and 0.5 L/h/kg, respectively. Approximately 75% of an oral dose of radiolabeled azelastine hydrochloride was excreted feces with less than 10% as unchanged azelastine. Azelastine is oxidatively metabolized principal active metabolite, desmethylazelastine, by the cytochrome P450 enzyme syster specific P450 isoforms responsible for the biotransformation of azelastine have not been identified; however, clinical interaction studies with the known CYP3A4 inhibitor erythrom failed to demonstrate a pharmacokinetic interaction. In a multiple-dose, steady-state drug interaction study in normal volunteers, cimetidine (400 mg twice daily), a nonspecific P45(inhibitor, raised orally administered mean azelastine (4 mg twice daily) concentrations by approximately 65%.

The major active metabolite, desmethylazelastine, was not measurable (below assay limi single-dose intranasal administration of azelastine hydrochloride. After intranasal dosing azelastine hydrochloride to steady-state, plasma concentrations of desmethylazelastine r

from 20-50% of azelastine concentrations. When azelastine hydrochloride is administerec desmethylazelastine has an elimination half-life of 54 hours. Limited data indicate that the metabolite profile is similar when azelastine hydrochloride is administered via the intranas oral route.

Pharmacology of Fluticasone Propionate
Fluticasone propionate is a synthetic, trifluorinated corticosteroid with anti-inflammatory a

In preclinical studies, fluticasone propionate revealed progesterone-like activity similar to natural hormone. However, the clinical significance of these findings in relation to the low levels is not known.

The precise mechanism through which fluticasone propionate affects allergic rhinitis symp not known. Corticosteroids have been shown to have a wide range of effects on multiple types (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and me (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in inflammation.

Pharmacokinetics:
Absorption: Fluticasone propionate delivered by the intranasal route has an absolute bioavailability averaging less than 2%. After intranasal treatment of patients with allergic r for 3 weeks, fluticasone propionate plasma concentrations were above the level of detecti pg/mL) only when recommended doses were exceeded and then only in occasional samp low plasma levels. Due to the low bioavailability by the intranasal route, the majority of the pharmacokinetic data was obtained via other routes of administration. Studies using oral of radiolabeled drug have demonstrated that fluticasone propionate is highly extracted fro plasma and absorption is low. Oral bioavailability is negligible, and the majority of the circ radioactivity is due to an inactive metabolite.

Distribution: Following intravenous administration, the initial disposition phase for flut propionate was rapid and consistent with its high lipid solubility and tissue binding. The vc distribution averaged 4.2 L/kg.

The percentage of fluticasone propionate bound to human plasma proteins averaged 91% obvious concentration relationship. Fluticasone propionate is weakly and reversibly bounc erythrocytes and freely equilibrates between erythrocytes and plasma. Fluticasone propio not significantly bound to human transcortin.

Metabolism: The total blood clearance of fluticasone propionate is high (average, 1,0 mL/min), with renal clearance accounting for less than 0.02% of the total. The only circula metabolite detected in man is the 17(beta)-carboxylic acid derivative of fluticasone propio which is formed through the cytochrome P450 3A4 pathway. This inactive metabolite had affinity (approximately 1/2,000) than the parent drug for the glucocorticoid receptor of hun cytosol in vitro and negligible pharmacological activity in animal studies. Other metabolite detected in vitro using cultured human hepatoma cells have not been detected in man.

Elimination: Following intravenous dosing, fluticasone propionate showed polyexpor kinetics and had a terminal elimination half-life of approximately 7.8 hours. Less than 5% radiolabeled oral dose was excreted in the urine as metabolites, with the remainder excre the feces as parent drug and metabolites.

Indications
Duonase is indicated for the management of symptoms of allergic rhinitis once the nee antihistamine and corticosteroid has been established. It is recommended to treat **mode severe persistent symptoms** in adults above 12 years. For children above 5 years **Duonase** is recommended for **severe symptoms** of allergic rhinitis. **Duonase** can used for treating non-allergic vasomotor rhinitis in adults and children 12 years of age anc

Dosage And Method of Administration
Adults and children 5 years and older: 1 spray/nostril twice daily

The recommended dosage should not be exceeded. Not recommended for use in childre 5 years.

Contact Us

Essential Update

News Update
HIV/AIDS Update
Respiratory Update
Cardiology Update
Infection Update
Neurology Update
Ophthalmology Update
Disease of the month
Medical Slides
Conferences

Therapeutic Index

Cipla
Cipla Omnicare

New Introductions

Internationally
Cipla
Protec

Essential Reading

Publications
Patient help
Treatment guidelines

Search:

Go

www
www.cipladoc.com

Contraindications

Duonase is contraindicated in patients with or known hypersensitivity to azelastine hydroc or fluticasone propionate or any of the components of the preparation.

Warnings and Precautions

- Concurrent use of this combination with alcohol or other CNS depressants or othe antihistamines should be avoided as additional reductions in alertness and additio impairment of CNS performance may occur due to azelastine.
- The replacement of a systemic corticosteroid with a topical corticosteroid can be accompanied by signs of adrenal insufficiency. Some patients may experience sy of withdrawal e.g. joint and/or muscular pain, lassitude and depression.
- The concomitant use of an intranasal corticosteroid with other corticosteroids coul increase the risk of signs or symptoms of hypercorticism and/ or suppression of th axis. Therefore the combination should be used cautiously in patients with other pathological conditions requiring steroids.
- Intranasal corticosteroids may cause a reduction in growth velocity when administ higher dose. The recommended dosage of **Duonase** should not be exceeded.
- Special care is needed in patients with lung tuberculosis and fungal and viral infec Children who are on immunosuppressant drugs are more susceptible to infections healthy children. Chicken pox and measles for example can have a more serious a fatal course in children on immunosuppressant corticosteroids.
- During long term therapy, monitoring of hematological and adrenal function is adv
- In clinical studies with intranasal fluticasone propionate, the development of localiz infections of the nose and the pharynx with *Candida albicans* has been seen rarel such an infection develops, it may require treatment with appropriate local therapy discontinuation of the treatment with **Duonase** is advised

Drug Interactions

The use of **Duonase** in patients taking concurrent drugs, which are potent inhibitors of tl cytochrome 450 3A4 system eg. Ketoconazole and protease inhibitors such as ritonavir m associated with increased systemic exposure of fluticasone.

Pregnancy

The combination should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation

It is not known whether azelastine hydrochloride or fluticasone propionate is excreted in h milk. Hence, caution should be exercised while prescribing this combination to nursing mo

Undesirable Effects

The most likely side effects with this combination are headache, somnolence, pharyngitis, epistaxis, nasal burning/irritation, nausea, vomiting, cough, taste disturbance. The combir may produce a bitter taste, which may lead to occasional nausea. Bitter taste disappears sometime.

Shelf Life

2 years

Storage and Handling Instructions

Store below 30 ^{0} C.
Do not refrigerate.
Protect from direct sunlight.

Packaging Information

Duonase Nasal Spray
Sales pack contains 70 metered doses

Last Updated: M

News Updates | Cardiology Update | Infection Update | Treatment Guidelines
Respiratory Update | Neurology Update | Ophthalmology Update | Medline |
Medical Slides | Patient Help | Conferences | Forum | Medical Quiz | New Introdu
Disease of the Month | Interesting Links | New Introductions Internationally | Car
Therapeutic Index | Cipla.com | Contact

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 10/518,016	Filing Date 07/06/2005	☒ To be Mailed

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☐		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	07/23/2009	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 36	Minus	** 51	= 0	X $ =		OR	X $52=	0
	Independent (37 CFR 1.16(h))	* 6	Minus	***3	= 3	X $ =		OR	X $220=	660
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	**660**

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/ANGELA D. JOHNSON/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
10/518,016	07/06/2005	Amar Lulla	PAC/20632 US (4137-04700)

CONFIRMATION NO. 4912

30652
CONLEY ROSE, P.C.
5601 GRANITE PARKWAY, SUITE 750
PLANO, TX 75024

POA ACCEPTANCE LETTER

OC000000035428575

Date Mailed: 04/13/2009

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 04/07/2009.

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.

/hgray/

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

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
10/518,016	07/06/2005	Amar Lulla	TPP31753

CONFIRMATION NO. 4912

POWER OF ATTORNEY NOTICE

77176
Novak, Druce & Quigg LLP
1300 I Street, N.W.
Suite 1000, West Tower
WASHINGTON, DC 20005

OC000000035428543

Date Mailed: 04/13/2009

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 04/07/2009.

- 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).

/hgray/

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

ELECTION UNDER 37 C.F.R. §§ 3.71 AND 3.73
AND POWER OF ATTORNEY

The undersigned, being ASSIGNEE of the entire interest in the following applications by virtue of an Assignment recorded in the United States Patent and Trademark Office as set forth below, hereby elects, under 37 C.F.R. § 3.71, to prosecute the applications to the exclusion of the inventor(s).

Application No.	Filing Date	Assignment Recordation Date	Reel/Frame	Atty. Docket No.
10/518,016	07/06/05	07/06/05	016833/0985	PAC/20632 US (4137-04700)
10/539,415	03/20/06	03/30/06	018884/0531	PAC/EHC/20668 US (4137-05000)
10/542,268	01/05/06	01/05/06	017992/0302	PAC/EHC/22452 US (4137-05100)
10/546,193	10/31/05	10/31/05	017875/0831	PAC/EHC/21233 US (4137-05200)
10/545,004	10/31/05	10/31/05	017291/0499	PAC/22565 US (4137-05300)
10/563,138	05/01/06	05/01/06	017883/0936	PAC/EHC/22985 US (4137-05400)
10/569,439	05/01/06	05/01/06	017883/0953	PAC/EHC/21835 US (4137-05500)

The ASSIGNEE hereby revokes any previous Powers of Attorney and appoints attorneys associated with Customer No.: **30652,** as its attorneys with full power of substitution and revocation, the substitutes being only partners or qualified members of staff of the attorneys associated with Customer No.: **30652,** to prosecute the application, to make alterations and amendments therein, to transact all business in the United States Patent and Trademark Office in connection therewith, to receive any Letters Patent, and for one year after issuance of such Letters Patent to file any request for a certificate of correction that may be deemed appropriate.

CIPLA LIMITED retains the right to revoke this Power of Attorney at any time and at its own discretion.

We declare that the below-named individual is authorized to execute this Power of Attorney on behalf of ASSIGNEE.

Pursuant to 37 C.F.R. § 3.73, the undersigned has reviewed the evidentiary documents, specifically the Assignment to CIPLA LIMITED referenced above, and certifies that to the best of my knowledge and belief, title remains in the name of the ASSIGNEE.

Please direct all communications to the address associated with Customer Number 30652.

ASSIGNEE: CIPLA LIMITED

By: _____
Amar Lulla, Joint Managing Director

Date: 25th March 2009

59423.02/4137.04700

PTO/SB/96 (03-09)
Approved for use through 04/30/2009. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Amar Lulla, et al.

Application No./Patent No.: 10/518,016 Filed/Issue Date: July 6, 2005

Titled: Combination of azelastine and steroids

CIPLA LIMITED , a corporation

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

states that it is:

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

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

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

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

A. ☒ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 016833, Frame 0985, or for which a copy therefore is attached.

OR

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

1. From: _____ 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(s).

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

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

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

/Rodney B. Carroll/ April 7, 2009

Signature Date

Rodney B. Carroll Attorney-in-Fact

Printed or Typed Name Title

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

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

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

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

Electronic Acknowledgement Receipt

EFS ID:	5111589
Application Number:	10518016
International Application Number:	
Confirmation Number:	4912
Title of Invention:	Combination of azelastine and steroids
First Named Inventor/Applicant Name:	Amar Lulla
Customer Number:	77176
Filer:	Rodney B. Carroll/Ellen Anderson
Filer Authorized By:	Rodney B. Carroll
Attorney Docket Number:	TPP31753
Receipt Date:	07-APR-2009
Filing Date:	06-JUL-2005
Time Stamp:	19:23:47
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Power of Attorney	ExecutedPOAforTransferredMatters.pdf	105143 6012b982bcc8f5f97dbaa69d54e3a8ecf3c2b86e	no	1

Warnings:	
Information:	000738

2	Assignee showing of ownership per 37 CFR 3.73(b).	StatementUnder37CFR373b.pdf	474470 6d51a96615e1b2bdcc1114a1b0a61e5ed6906630	no	2

Warnings:	
Information:	
Total Files Size (in bytes):	579613

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/518,016	07/06/2005	Amar Lulla	TPP31753	4912

77176 7590 01/23/2009

Novak, Druce & Quigg LLP
1300 I Street, N.W.
Suite 1000, West Tower
WASHINGTON, DC 20005

EXAMINER
BROOKS, KRISTIE LATRICE

ART UNIT	PAPER NUMBER
1616	

MAIL DATE	DELIVERY MODE
01/23/2009	PAPER

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

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

Office Action Summary	Application No.	Applicant(s)	
	10/518,016	LULLA ET AL.	
	Examiner	Art Unit	
	KRISTIE L. BROOKS	1616	

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

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 July 2005*.

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) *1-42 and 44-52* is/are pending in the application.

4a) Of the above claim(s) *23,24 and 46-52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22,25-42,44 and 45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

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

Application Papers

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

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

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

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/6/05;10/5/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The previous non-final office action mailed October 17, 2008 is hereby **vacated** and a new office action is presented below.

Election/Restrictions

2. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-22, and 2542 and 44-45 are drawn to a pharmaceutical formulation comprising azelastine and a steroid, classified in class 514, subclass 171.

II. Claims 23-24 are drawn to drawn to a pressure packing, classified in class 128, subclass 200.23.

III. Claims 46-52 are drawn to a method of use, classified in class 514, subclass 171.

The inventions are distinct, each from the other because of the following reasons:

Inventions I and II are directed to related products. The related inventions are distinct if: (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed do not overlap in scope because the two inventions have materially different design and mode of operation. Invention II is drawn to a pressure packing device or metered dose inhaler where a composition is delivered by spray or

aerosol which is different from the pharmaceutical formulation of Invention I. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

Inventions I and III are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case, the product of invention I can be used in a materially different process, such as, improving vision .

Inventions II and III are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case, the process of Invention III, can be used with a materially different product, such as, without the pressure packing device or metered dose inhaler of Invention II.

3. For purpose of examination, the Examiner has requested Applicant to provisionally elect a single steroid selected from: beclomethasone, mometasone, fluticasone, or a pharmaceutically acceptable ester thereof, budesonide or cyclosenide.

4. Restriction for examination purposes as indicated is proper because all these inventions listed in this action are independent or distinct for the reasons given above and there would be a serious search and examination burden if restriction were not required because one or more of the following reasons apply:

(a) the inventions have acquired a separate status in the art in view of their different classification;

(b) the inventions have acquired a separate status in the art due to their recognized divergent subject matter;

(c) the inventions require a different field of search (for example, searching different classes/subclasses or electronic resources, or employing different search queries);

(d) the prior art applicable to one invention would not likely be applicable to another invention;

(e) the inventions are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a invention to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected invention**.

The election of an invention may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election

shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected invention.

If claims are added after the election, applicant must indicate which of these claims are readable upon the elected invention.

Should applicant traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

5. The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise

require all the limitations of the allowable product claim will be considered for rejoinder. All claims directed to a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder**. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Telephone Election

6. During a telephone conversation with Attorney Tom Pavelko on May 21, 2008 a provisional election was made without traverse to prosecute Invention I, claims 1-22, 25-42 and 44-45. A provisional election of species of fluticasone was also made.

Affirmation of this election must be made by applicant in replying to this Office action. Claims 23-24, 32-34, 39-42 and 46-52 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Status of Application

7. Claims 1-42 and 44-52 are pending.

8. Claims 23-24, 32-34, 39-42 and 46-52 are withdrawn from further consideration as being drawn to the non-elected invention.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 6 and 18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 6 is indefinite due to the phrase "less than about 10μm," which simultaneously refers to a broad range and a narrower range. For example, in claim 2, the conflicting phrase "less than about 10μm " is unclear as to whether it is less than 10μm, in which the range cannot be greater than 10μm, or about 10μm thereof, in which the range can include a value above 10μm. Therefore, it would be unclear to a skilled artisan, which range Applicant has intended.

For purposes of examination, the Examiner has interpreted "less than about 10μm thereof" to mean less than 10μm.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). **In the present instance,** claim 18 recites "…wherein the buffer maintains a pH of the aqueous phase at from 3 to 7…", and the claim also recites phrases "preferably 4.5 to about 6", which is the narrower statement of the range/limitation.

Claim Rejections - 35 USC § 102

11. 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.

12. Claims 1-4, 7,9-10,12-21, 30-32, and 44-45 are rejected under 35 U.S.C. 102(b) as being anticipated by Cramer (EP 0780127).

Cramer teaches a nasal spray composition comprising about 0.001 to about 0.2% concentration of a glucocorticosteroid (i.e. beclomethasone, flunisolide, triamcinolone, fluticasone, mometasone, bedusonide and pharmaceutically acceptable salts), 0.01 to about 4% concentration of an antihistamine (i.e. azelastine or

pharmaceutically acceptable salt thereof), and an intranasal carrier (see the abstract and page 2 lines 36-45). The composition may contain isotonic agents such as citric acid, boric acid, propylene glycol, etc., thickening agents such as xanthan gum, microcrystalline cellulose, carboxymethyl cellulose, hydroxypropyl cellulose, etc., humectants such as sorbitol, propylene glycol, polyethylene glycol, etc. and preservatives such as benzyl alcohol, phenylethyl alcohol, and quaternary ammoniums such as benzalkonium chloride (see page 4 lines 50-58 and page 5 lines 1-22). The pH of the composition is from about 4.5 to about 9 (see page 2 lines 57-58). The composition may be formulated into a nasal solution (for use as drops or a spray), a nasal suspension, ointment, or gel (see page 3 lines 43-47). Typically the dosage units may be prepared to deliver 0.5mcg to about 100mcg of the glucocorticoid and 5mcg to about 1000mcg of the antihistamine spray (see page 3 lines 58 and page 4 lines 1-2). Example III discloses an intranasal pharmaceutical composition prepared by combining the following components utilizing conventional mixing techniques, shown below:

Component	Wgt %
triamcinolone acetonide	0.050
azelastine HCl	0.070
polysorbate 80	0.050
glycerin	2.000
hydroxypropyl methyl cellulose	1.000
sodium chloride	0.900
ethylenediamine tetraacetic acid	0.050
benzalkonium chloride	0.020
distilled water	q.s. to vol.

(see page 6, Example III).

Claim Rejections - 35 USC § 103

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

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

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

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

14. Claims 5 and 35-38 are rejected under U.S.C. 103(a) as being unpatentable over Cramer (EP 0780127).

Applicant claims a pharmaceutical formulation which comprises azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof and a steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, preferably the formulation being in a form suitable for nasal or ocular administration.

Determination of the scope and content of the prior art (MPEP 2141.01)

Cramer teaches a nasal spray composition comprising about 0.001 to about 0.2% concentration of a glucocorticosteroid (i.e. beclomethasone, flunisolide, triamcinolone, fluticasone, mometasone, bedusonide and pharmaceutically acceptable salts), 0.01 to about 4% concentration of an antihistamine (i.e. azelastine or pharmaceutically acceptable salt thereof, and an intranasal carrier (see the abstract and page 2 lines 36-45). The composition may contain isotonic agents such as citric acid, boric acid, propylene glycol, etc., thickening agents such as xanthan gum, microcrystalline cellulose, carboxymethyl cellulose, hydroxypropyl cellulose, etc., humectants such as sorbitol, propylene glycol, polyethylene glycol, etc. and preservatives such as benzyl alcohol, phenylethyl alcohol, and quaternary ammoniums such as benzalkonium chloride (see page 4 lines 50-58 and page 5 lines 1-22). The pH of the composition is from about 4.5 to about 9 (see page 2 lines 57-58). The composition may be formulated into a nasal solution (for use as drops or a spray), a nasal suspension, ointment, or gel (see page 3 lines 43-47). Typically the dosage units may be prepared to deliver 0.5mcg to about 100mcg of the glucocorticoid and 5mcg to about 1000mcg of the antihistamine spray (see page 3 lines 58 and page 4 lines 1-2). Example III discloses an intranasal pharmaceutical composition prepared by combining the following components utilizing conventional mixing techniques, shown below:

Component	Wgt %
triamcinolone acetonide	0.050
azelastine HCl	0.070
polysorbate 80	0.050
glycerin	2.000
hydroxypropyl methyl cellulose	1.000
sodium chloride	0.900
ethylenediamine tetraacetic acid	0.050
benzalkonium chloride	0.020
distilled water	q.s. to vol.

(see page 6, Example III).

Ascertainment of the difference between the prior art and the claims (MPEP 2141.02)

Cramer does not exemplify a composition comprising azelastine and fluticasone.

Finding of prima facie obviousness Rational and Motivation (MPEP 2142-2143)

However, one of ordinary skill in the art would have been motivated to make a composition comprising azelastine and fluticasone because Cramer suggests that the combination of a glucocorticoid (i.e. fluticasone) and antihistamine (i.e. azelastine) provide improved relief of symptoms associated with seasonal or perennial allergic rhinoconjunctivitis.

Thus, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to make a composition comprising azelastine and fluticasone for the purpose of providing intranasal compositions with improves effectiveness in the treatment of seasonal or perennial allergic rhinoconjunctivitis.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made because the prior art is fairly suggestive of the claimed invention.

15. Claims 22 and 26-27 are rejected under U.S.C. 103(a) as being unpatentable over Cramer (EP 0780127) in view of Modi (US 6,294,153).

Applicant claims a pharmaceutical formulation which comprises azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof and a steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, preferably the formulation being in a form suitable for nasal or ocular administration.

Determination of the scope and content of the prior art (MPEP 2141.01)

Cramer teaches a nasal spray composition comprising about 0.001 to about 0.2% concentration of a glucocorticosteroid (i.e. beclomethasone, flunisolide, triamcinolone, fluticasone, mometasone, bedusonide and pharmaceutically acceptable salts), 0.01 to about 4% concentration of an antihistamine (i.e. azelastine or pharmaceutically acceptable salt thereof, and an intranasal carrier (see the abstract and page 2 lines 36-45). The composition may contain isotonic agents such as citric acid, boric acid, propylene glycol, etc., thickening agents such as xanthan gum,

microcrystalline cellulose, carboxymethyl cellulose, hydroxypropyl cellulose, etc., humectants such as sorbitol, propylene glycol, polyethylene glycol, etc. and preservatives such as benzyl alcohol, phenylethyl alcohol, and quaternary ammoniums such as benzalkonium chloride (see page 4 lines 50-58 and page 5 lines 1-22). The pH of the composition is from about 4.5 to about 9 (see page 2 lines 57-58). The composition may be formulated into a nasal solution (for use as drops or a spray), a nasal suspension, ointment, or gel (see page 3 lines 43-47). Typically the dosage units may be prepared to deliver 0.5mcg to about 100mcg of the glucocorticoid and 5mcg to about 1000mcg of the antihistamine spray (see page 3 lines 58 and page 4 lines 1-2). Example III discloses an intranasal pharmaceutical composition prepared by combining the following components utilizing conventional mixing techniques, shown below:

Component	Wgt %
triamcinolone acetonide	0.050
azelastine HCl	0.070
polysorbate 80	0.050
glycerin	2.000
hydroxypropyl methyl cellulose	1.000
sodium chloride	0.900
ethylenediamine tetraacetic acid	0.050
benzalkonium chloride	0.020
distilled water	q.s. to vol.

(see page 6, Example III).

Ascertainment of the difference between the prior art and the claims (MPEP 2141.02)

Cramer does not exemplify a nasal composition further comprising a propellant. This deficiency is cured by the teachings of Modi.

Modi teaches aerosol formulations for nasal delivery comprising pharmaceutical agents (i.e. anti-inflammatories, steroids, etc.), water, excipients and a propellant (see the abstract and column 3 lines 30-40). Improved penetration and absorption of the formulations can be achieved by mixing the formulation with propellants such as tetrafluroethane, etc., especially when delivered through aerosol devices (i.e. MDI). (see column 2 lines 5-24).

Finding of prima facie obviousness Rational and Motivation (MPEP 2142-2143)

One of ordinary skill in the art would have been motivated to make a composition further comprising a propellant because Modi suggests that adding propellants to nasal formulations can increase penetration and absorption in the nasal cavity.

Thus, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to make a composition further comprising a propellant for the purpose of increasing penetration of active formulations into the nasal cavity.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made because the prior art is fairly suggestive of the claimed invention.

16. Claims 1-3 and 6 are rejected under U.S.C. 103(a) as being unpatentable over Malmqvist-Granlund et al. (US 6,391,340).

Applicant claims a pharmaceutical formulation which comprises azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof and a steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, preferably the formulation being in a form suitable for nasal or ocular administration.

Determination of the scope and content of the prior art (MPEP 2141.01)

Malmqvist-Granlund et al. teach a dry powder solid particulate pharmaceutical formulation suitable for application to the nose comprising finely divided drug particles and a carrier, where at least 70% of the drug particles have a size below 15μm (see the abstract and column 1 lines 52-62). The drugs that are used are classes of drugs used to treat conditions of the nose such as antihistamines (i.e. azelastine) and anti-inflammatories (i.e. fluticasone) and mixtures thereof (see column 2 lines 36-40). Salts, hydrates, solvates and esters of the drugs can also be used (see column 2 lines 36-42).

Ascertainment of the difference between the prior art and the claims (MPEP 2141.02)

Malmqvist-Granlund et al. do not exemplify a dry powder composition comprising azelastine and a steroid with a particle size of less than 10μm.

Finding of prima facie obviousness Rational and Motivation (MPEP 2142-2143)

However, one of ordinary skill in the art would have been motivated to make a composition comprising azelastine and a steroid because Malmqvist-Granlund et al. suggest a dry powder formulation with a particle size of less than 15μm comprising a anti-inflammatory (i.e. fluticasone) and a antihistamine (i.e. azelastine), which will disperse evenly over the nasal mucosa.

Thus, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to make a composition comprising azelastine and a steroid for the purpose of obtaining the benefits for the nose from such a combination and for increased delivery to the nasal mucosa.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made because the prior art is fairly suggestive of the claimed invention.

17. Claims 28-29 are rejected under U.S.C. 103(a) as being unpatentable over Cramer (EP 0780127) in view of Alfonso et al. (US 6,017,963).

Applicant claims a pharmaceutical formulation which comprises azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof and a steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, preferably the formulation being in a form suitable for nasal or ocular administration.

Determination of the scope and content of the prior art (MPEP 2141.01)

Cramer teaches a nasal spray composition comprising about 0.001 to about 0.2% concentration of a glucocorticosteroid (i.e. beclomethasone, flunisolide, triamcinolone, fluticasone, mometasone, bedusonide and pharmaceutically acceptable salts), 0.01 to about 4% concentration of an antihistamine (i.e. azelastine or pharmaceutically acceptable salt thereof, and an intranasal carrier (see the abstract and page 2 lines 36-45). The composition may contain isotonic agents such as citric acid, boric acid, propylene glycol, etc., thickening agents such as xanthan gum, microcrystalline cellulose, carboxymethyl cellulose, hydroxypropyl cellulose, etc., humectants such as sorbitol, propylene glycol, polyethylene glycol, etc. and preservatives such as benzyl alcohol, phenylethyl alcohol, and quaternary ammoniums such as benzalkonium chloride (see page 4 lines 50-58 and page 5 lines 1-22). The pH of the composition is from about 4.5 to about 9 (see page 2 lines 57-58). The composition may be formulated into a nasal solution (for use as drops or a spray), a nasal suspension, ointment, or gel (see page 3 lines 43-47). Typically the dosage units may be prepared to deliver 0.5mcg to about 100mcg of the glucocorticoid and 5mcg to about 1000mcg of the antihistamine spray (see page 3 lines 58 and page 4 lines 1-2). Example III discloses an intranasal pharmaceutical composition prepared by combining the following components utilizing conventional mixing techniques, shown below:

Component	Wgt %
triamcinolone acetonide	0.050
azelastine HCl	0.070
polysorbate 80	0.050
glycerin	2.000
hydroxypropyl methyl cellulose	1.000
sodium chloride	0.900
ethylenediamine tetraacetic acid	0.050
benzalkonium chloride	0.020
distilled water	q.s. to vol.

(see page 6, Example III).

Ascertainment of the difference between the prior art and the claims (MPEP 2141.02)

Cramer does not exemplify a nasal composition further comprising a propellant. This deficiency is cured by the teachings of Alfonso et al.

Alfonso et al. teaches intranasal and/or inhalation administration of pharmaceutical agents (see the abstract). The dosage form suitable for intranasal and/or inhalation administration can be in the form of a liquid solution suspension, insufflation powder, etc. for administration as a nasal spray, drop or inhaled fine particles (i.e. insuflation) (see column 3 lines 1-65, column 5 lines 36-45, and column 7 lines 1-26).

Finding of prima facie obviousness Rational and Motivation (MPEP 2142-2143)

One of ordinary skill in the art would have been motivated to make the instant composition in the form of an insufflation powder because Alfonso et al. suggest the nasal compositions in the form of a spray, droplet, insufflation powder, etc.

Thus, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to make the instant composition in the form of an insufflation powder because it is an obvious variation of ways to administer a nasal composition as suggested Alfonso et al.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made because the prior art is fairly suggestive of the claimed invention.

Conclusion

18. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KRISTIE L. BROOKS whose telephone number is (571)272-9072. The examiner can normally be reached on M-F 8:30am-6:00pm Est..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann R. Richter can be reached on (571) 272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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

KB

/Mina Haghighatian/
Primary Examiner, Art Unit 1616

Notice of References Cited	Application/Control No. 10/518,016	Applicant(s)/Patent Under Reexamination LULLA ET AL.	
	Examiner KRISTIE L. BROOKS	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-6,391,340	05-2002	Malmqvist-Granlund et al.	424/489
*	B	US-6,294,153	09-2001	Modi, Pankaj	424/45
*	C	US-6,017,963	01-2000	Alfonso et al.	514/646
	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	EP 0780127	06-1997		Cramer	
	O					
	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.

JPW/1614

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of

Amar LULLA et al — Group Art Unit: 1614

Serial No.: 10/518,016 — Examiner: Unassigned

Filed: July 6, 2005 — Confirmation No. 4912

For: COMBINATION OF AZELASTINE AND STEROIDS

INFORMATION DISCLOSURE STATEMENT

Commissioner of Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

Pursuant to Rules 56 and 98, Applicants hereby call the attention of the Patent Office to the references listed on the attached Form PTO 1449. These references were cited in an International Search Report (copy enclosed) issued in connection with the corresponding international application.

Applicants present these references so that the Patent Office may, in the first instance, determine any relevancy thereof to the presently claimed invention, see Beckman Instruments, Inc. v. Chemtronics, Inc., 439 F.2d 1369, 1380, 165 USPQ 355, 364 (5th Cir. 1970).

Applicants respectfully request that these references be expressly considered during the prosecution of this application and made of record herein and appear among the "References Cited" on any patent to issue herefrom.

Respectfully submitted,

TPP/mtw
Attorney Docket No.: TPP 31753

Thomas P. Pavelko
Registration No. 31,689

STEVENS, DAVIS, MILLER & MOSHER, L.L.P.
1615 L Street, N.W., Suite 850
Washington, D.C. 20036
Telephone: (202) 785-0100
Facsimile: (202) 785-0100 or (202) 785-0200

Date: October 5, 2005

FORM PTO-1449 (Rev. 4/92) U.S. Department of Commerce Patent and Trademark Office	ATTY. DOCKET NO. TPP 31753	SERIAL NO. 10/518,016
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use several sheets if necessary)	APPLICANT Amar LULLA et al	
	FILING DATE July 6, 2005	GROUP 1614

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
/K.B./		9 7 0 1 3 3 7	01/97	WO				
/K.B./		0 7 8 0 1 2 7	06/97	EP				
/K.B./		9 8 4 8 8 3 9	11/98	WO				
/K.B./	1	9 9 4 7 2 3 4	04/01	DE				

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

/K.B./		Database Medline "Online! US National Library of Medicine (NLM), Bethesda, MD, US: 2000 Portmann D et al: "Acceptability of local treatment of allergic rhinitis with a combination of a corticoid (beclomethasone) and an antihistaminic (azelastine); vol. 121, no. 4, 2000, pages 273-279
/K.B./		Busse W W et al: "Corticosteroid-Sparing Effect of Azelastine in the Management of Bronchial Asthma" - American Journal of Respiratory and Critical Care Medicine, American Lung Association, new York, NW, vol. 153, no. 1, 1996, pages 122-172, page 127, column 1, paragraph 2
/K.B./		International Search Report under Section 17 UK Patent Office collections, including GB, EP, WO & US patent specifications

EXAMINER /Kristie Brooks/	DATE CONSIDERED 09/23/2008

EXAMINER: Initial if citation is considered, draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

(Form PTO-1449 [6-4])

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of

Amar LULLA et al

Group Art Unit: Unassigned

Serial No.: 10/518,016

Examiner: Unassigned

Filed: December 14, 2004

Confirmation No. 4912

For: COMBINATION OF AZELASTINE AND STEROIDS

INFORMATION DISCLOSURE STATEMENT

Commissioner of Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

Pursuant to Rules 56 and 98, Applicants hereby call the attention of the Patent Office to the references listed on the attached Form PTO 1449. These references were cited in an International Search Report issued in connection with the corresponding international application.

Applicants present these references so that the Patent Office may, in the first instance, determine any relevancy thereof to the presently claimed invention, see Beckman Instruments, Inc. v. Chemtronics, Inc., 439 F.2d 1369, 1380, 165 USPQ 355, 364 (5th Cir. 1970).

Applicants respectfully request that these references be expressly considered during the prosecution of this application and made of record herein and appear among the "References Cited" on any patent to issue herefrom.

Respectfully submitted,

TPP/mat
Attorney Docket No.: TPP 31753

Thomas P. Pavelko
Registration No. 31,689

STEVENS, DAVIS, MILLER & MOSHER, L.L.P.
1615 L Street, N.W., Suite 850
Washington, D.C. 20036
Telephone: (202) 785-0100
Facsimile: (202) 408-5200 or (202) 408-5088

Date: July 6, 2005

FORM PTO-1449 (Rev. 4/92) U.S. Department of Commerce Patent and Trademark Office	ATTY. DOCKET NO. TPP 31753	SERIAL NO. 10/518,016
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use several sheets if necessary)	APPLICANT Amar LULLA et al	
	FILING DATE December 14, 2004	GROUP Applications

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION	
							YES	NO
/K.B./		9 7 0 1 3 3 7	01/97	WO				
/K.B./		0 7 8 0 1 2 7	06/97	EP				

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

		Database Medline "Online! US National Library of Medicine (NLM), Bethesda, MD, US: 2000 Portmann D et al: "Acceptability of local treatment of allergic rhinitis with a combination of a corticoid (beclomethasone) and an antihistaminic (azelastine); vol. 121, no. 4, 2000, pages 273-279
		Busse W W et al: "Corticosteroid-Sparing Effect of Azelastine in the Management of Bronchial Asthma" - American Journal of Respiratory and Critical Care Medicine, American Lung Association, new York, NW, vol. 153, no. 1, 1996, pages 122-172, page 127, column 1, paragraph 2

EXAMINER	/Kristie Brooks/	DATE CONSIDERED	09/23/2008

EXAMINER: Initial if citation is considered, draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

(Form PTO-1449 [6-4])

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10518016	LULLA ET AL.
	Examiner	Art Unit
	KRISTIE L BROOKS	1616

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

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

CLAIM		DATE								
Final	Original	09/23/2008	01/21/2009							
	1	✓	✓							
	2	✓	✓							
	3	✓	✓							
	4	✓	✓							
	5	✓	✓							
	6	✓	✓							
	7	✓	✓							
	8	✓	✓							
	9	✓	✓							
	10	✓	✓							
	11	✓	✓							
	12	✓	✓							
	13	✓	✓							
	14	✓	✓							
	15	✓	✓							
	16	✓	✓							
	17	✓	✓							
	18	✓	✓							
	19	✓	✓							
	20	✓	✓							
	21	✓	✓							
	22	✓	✓							
	23	N	N							
	24	N	N							
	25	✓	✓							
	26	✓	✓							
	27	✓	✓							
	28	✓	✓							
	29	✓	✓							
	30	✓	✓							
	31	✓	✓							
	32	✓	✓							
	33	✓	✓							
	34	✓	✓							
	35	✓	✓							
	36	✓	✓							

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10518016	LULLA ET AL.
	Examiner	Art Unit
	KRISTIE L BROOKS	1616

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

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

CLAIM		DATE								
Final	Original	09/23/2008	01/21/2009							
	37	✓	✓							
	38	✓	✓							
	39	✓	✓							
	40	✓	✓							
	41	✓	✓							
	42	✓	✓							
	43	✓	-							
	44	✓	✓							
	45	✓	✓							
	46	N	N							
	47	N	N							
	48	N	N							
	49	N	N							
	50	N	N							
	51		N							
	52		N							

UNITED STATES PATENT AND TRADEMARK OFFICE

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

BIB DATA SHEET

CONFIRMATION NO. 4912

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
10/518,016	07/06/2005 RULE	514	1616	TPP31753

APPLICANTS

Amar Lulla, Mumbai, INDIA;
Geena Malhotra, Mumbai, INDIA;

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

This application is a 371 of PCT/GB03/02557 06/13/2003

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

UNITED KINGDOM 0213739.6 06/14/2002

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

Foreign Priority claimed ☑ Yes ☐ No 35 USC 119(a-d) conditions met ☑ Yes ☐ No Verified and Acknowledged /Kristie L. Brooks/ Examiner's Signature	☐ Met after Allowance KB Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		INDIA	0	51	3

ADDRESS

Novak, Druce & Quigg LLP
1300 I Street, N.W.
Suite 1000, West Tower
WASHINGTON, DC 20005
UNITED STATES

TITLE

Combination of azelastine and steroids

FILING FEE RECEIVED		
2580	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/518,016	07/06/2005	Amar Lulla	TPP31753	4912

77176 7590 10/17/2008

Novak, Druce & Quigg LLP
1300 I Street, N.W.
Suite 1000, West Tower
WASHINGTON, DC 20005

EXAMINER	
BROOKS, KRISTIE LATRICE	
ART UNIT	**PAPER NUMBER**
1616	

MAIL DATE	DELIVERY MODE
10/17/2008	PAPER

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

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

Office Action Summary	Application No.	Applicant(s)	
	10/518,016	LULLA ET AL.	
	Examiner	Art Unit	
	KRISTIE L. BROOKS	1616	

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

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *1-22, 25-42, and 44-45*.

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) *1-50* is/are pending in the application.

4a) Of the above claim(s) *23,24,43 and 46-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22,25-42,44 and 45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-50* are subject to restriction and/or election requirement.

Application Papers

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

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

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

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/5/05; 7/6/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

   I. Claims 1-22, and 25-45 are drawn to a pharmaceutical formulation comprising azelastine and a steroid, classified in class 514, subclass 171.

   II. Claims 23-24 are drawn to drawn to a pressure packing, classified in class 128, subclass 200.23.

   III. Claims 46-50 are drawn to a method of use, classified in class 514, subclass 171.

The inventions are distinct, each from the other because of the following reasons:

Inventions I and II are directed to related products. The related inventions are distinct if: (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed do not overlap in scope because the two inventions have materially different design and mode of operation. Invention II is drawn to a pressure packing device or metered dose inhaler where a composition is delivered by spray or aerosol which is different from the pharmaceutical formulation of Invention I. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

Inventions I and III are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case, the product of invention I can be used in a materially different process, such as, improving vision .

Inventions II and III are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case, the process of Invention III, can be used with a materially different product, such as, without the pressure packing device or metered dose inhaler of Invention II.

2. For purpose of examination, the Examiner has requested Applicant to provisionally elect a single steroid selected from: beclomethasone, mometasone, fluticasone, or a pharmaceutically acceptable ester thereof, budesonide or cyclosenide.

3. Restriction for examination purposes as indicated is proper because all these inventions listed in this action are independent or distinct for the reasons given above

and there would be a serious search and examination burden if restriction were not required because one or more of the following reasons apply:

(a) the inventions have acquired a separate status in the art in view of their different classification;

(b) the inventions have acquired a separate status in the art due to their recognized divergent subject matter;

(c) the inventions require a different field of search (for example, searching different classes/subclasses or electronic resources, or employing different search queries);

(d) the prior art applicable to one invention would not likely be applicable to another invention;

(e) the inventions are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a invention to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected invention**.

The election of an invention may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement

will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected invention.

If claims are added after the election, applicant must indicate which of these claims are readable upon the elected invention.

Should applicant traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

4. The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder.

All claims directed to a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder**. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Telephone Election

5. During a telephone conversation with Attorney Tom Pavelko on May 21, 2008 a provisional election was made without traverse to prosecute Invention I, claims 1-22 and 25-45. A provisional election of species of fluticasone was also made.

Affirmation of this election must be made by applicant in replying to this Office action. Claims 23-24, 32-34, 39-42 and 46-50 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Status of Application

6. Claims 1-50 are pending.

7. Claims 23-24, 32-34, 39-42 and 46-50 are withdrawn from further consideration as being drawn to the non-elected invention.

Claim Objections

8. Claims 5-22 and 45 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim. See MPEP § 608.01(n).

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 6, 18 and 43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). **In the present instance, claim 6** recites the broad recitation “wherein the formulation particle size of less than 10 μm”, and the claim also recites phrases "preferably less than 5 μm”, which is the narrower statement of the range/limitation.

Claim 18 recites “…wherein the buffer maintains a pH of the aqueous phase at from 3 to 7…”, and the claim also recites phrases “preferably 4.5 to about 6”, which is the narrower statement of the range/limitation.

Claim 18 is also indefinite due to the phrase "less than about 10μm,” which simultaneously refers to a broad range and a narrower range. For example, in claim 2, the conflicting phrase "less than about 10μm " is unclear as to whether it is less than 10μm, in which the range cannot be greater than 10μm, or about 10μm thereof, in which the range can include a value above 10μm. Therefore, it would be unclear to a skilled artisan, which range Applicant has intended.

For purposes of examination, the Examiner has interpreted "less than about 10μm thereof" to mean less than 10μm.

Claim 43 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite in that it fails to point out what is included or excluded by the claim language.

The claim refers to formulations described in the Examples of the specification. It is unclear what is encompassed by the claim and what is included in the formulations. This claim is an omnibus type claim.

Claim Rejections - 35 USC § 102

11. 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.

12. Claims 1-4, 7,9-10,12-21, 30-32, and 44-45 are rejected under 35 U.S.C. 102(b) as being anticipated by Cramer (EP 0780127).

Cramer teaches a nasal spray composition comprising about 0.001 to about 0.2% concentration of a glucocorticosteroid (i.e. beclomethasone, flunisolide, triamcinolone, fluticasone, mometasone, bedusonide and pharmaceutically acceptable salts), 0.01 to about 4% concentration of an antihistamine (i.e. azelastine or pharmaceutically acceptable salt thereof), and an intranasal carrier (see the abstract and page 2 lines 36-45). The composition may contain isotonic agents such as citric acid, boric acid, propylene glycol, etc., thickening agents such as xanthan gum, microcrystalline cellulose, carboxymethyl cellulose, hydroxypropyl cellulose, etc., humectants such as sorbitol, propylene glycol, polyethylene glycol, etc. and preservatives such as benzyl alcohol, phenylethyl alcohol, and quaternary ammoniums such as benzalkonium chloride (see page 4 lines 50-58 and page 5 lines 1-22). The pH

of the composition is from about 4.5 to about 9 (see page 2 lines 57-58). The composition may be formulated into a nasal solution (for use as drops or a spray), a nasal suspension, ointment, or gel (see page 3 lines 43-47). Typically the dosage units may be prepared to deliver 0.5mcg to about 100mcg of the glucocorticoid and 5mcg to about 1000mcg of the antihistamine spray (see page 3 lines 58 and page 4 lines 1-2). Example III discloses an intranasal pharmaceutical composition prepared by combining the following components utilizing conventional mixing techniques, shown below:

Component	Wgt %
triamcinolone acetonide	0.050
azelastine HCl	0.070
polysorbate 80	0.050
glycerin	2.000
hydroxypropyl methyl cellulose	1.000
sodium chloride	0.500
ethylenediamine tetraacetic acid	0.050
benzalkonium chloride	0.020
distilled water	q.s. to vol.

(see page 6, Example III).

Claim Rejections - 35 USC § 103

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

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

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

1. Determining the scope and contents of the prior art.

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

14. Claims 5, 35-38 and 43 are rejected under U.S.C. 103(a) as being unpatentable over Cramer (EP 0780127).

Applicant claims a pharmaceutical formulation which comprises azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof and a steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, preferably the formulation being in a form suitable for nasal or ocular administration.

Determination of the scope and content of the prior art (MPEP 2141.01)

Cramer teaches a nasal spray composition comprising about 0.001 to about 0.2% concentration of a glucocorticosteroid (i.e. beclomethasone, flunisolide, triamcinolone, fluticasone, mometasone, bedusonide and pharmaceutically acceptable salts), 0.01 to about 4% concentration of an antihistamine (i.e. azelastine or pharmaceutically acceptable salt thereof, and an intranasal carrier (see the abstract and page 2 lines 36-45). The composition may contain isotonic agents such as citric acid, boric acid, propylene glycol, etc., thickening agents such as xanthan gum, microcrystalline cellulose, carboxymethyl cellulose, hydroxypropyl cellulose, etc.,

humectants such as sorbitol, propylene glycol, polyethylene glycol, etc. and preservatives such as benzyl alcohol, phenylethyl alcohol, and quaternary ammoniums such as benzalkonium chloride (see page 4 lines 50-58 and page 5 lines 1-22). The pH of the composition is from about 4.5 to about 9 (see page 2 lines 57-58). The composition may be formulated into a nasal solution (for use as drops or a spray), a nasal suspension, ointment, or gel (see page 3 lines 43-47). Typically the dosage units may be prepared to deliver 0.5mcg to about 100mcg of the glucocorticoid and 5mcg to about 1000mcg of the antihistamine spray (see page 3 lines 58 and page 4 lines 1-2). Example III discloses an intranasal pharmaceutical composition prepared by combining the following components utilizing conventional mixing techniques, shown below:

Component	Wgt %
triamcinolone acetonide	0.050
azelastine HCl	0.070
polysorbate 80	0.050
glycerin	2.000
hydroxypropyl methyl cellulose	1.000
sodium chloride	0.900
ethylenediamine tetraacetic acid	0.050
benzalkonium chloride	0.020
distilled water	q.s. to vol.

(see page 6, Example III).

Ascertainment of the difference between the prior art and the claims (MPEP 2141.02)

Cramer does not exemplify a composition comprising azelastine and fluticasone.

Finding of prima facie obviousness Rational and Motivation (MPEP 2142-2143)

However, one of ordinary skill in the art would have been motivated to make a composition comprising azelastine and fluticasone because Cramer suggests that the combination of a glucocorticoid (i.e. fluticasone) and antihistamine (i.e. azelastine) provide improved relief of symptoms associated with seasonal or perennial allergic rhinoconjunctivitis.

Thus, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to make a composition comprising azelastine and fluticasone for the purpose of providing intranasal compositions with improves effectiveness in the treatment of seasonal or perennial allergic rhinoconjunctivitis.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made because the prior art is fairly suggestive of the claimed invention.

15. Claims 22 and 26-27 are rejected under U.S.C. 103(a) as being unpatentable over Cramer (EP 0780127) in view of Modi (US 6,294,153).

Applicant claims a pharmaceutical formulation which comprises azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof and a steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, preferably the formulation being in a form suitable for nasal or ocular administration.

Determination of the scope and content of the prior art (MPEP 2141.01)

Cramer teaches a nasal spray composition comprising about 0.001 to about 0.2% concentration of a glucocorticosteroid (i.e. beclomethasone, flunisolide, triamcinolone, fluticasone, mometasone, bedusonide and pharmaceutically acceptable salts), 0.01 to about 4% concentration of an antihistamine (i.e. azelastine or pharmaceutically acceptable salt thereof, and an intranasal carrier (see the abstract and page 2 lines 36-45). The composition may contain isotonic agents such as citric acid, boric acid, propylene glycol, etc., thickening agents such as xanthan gum, microcrystalline cellulose, carboxymethyl cellulose, hydroxypropyl cellulose, etc., humectants such as sorbitol, propylene glycol, polyethylene glycol, etc. and preservatives such as benzyl alcohol, phenylethyl alcohol, and quaternary ammoniums such as benzalkonium chloride (see page 4 lines 50-58 and page 5 lines 1-22). The pH of the composition is from about 4.5 to about 9 (see page 2 lines 57-58). The composition may be formulated into a nasal solution (for use as drops or a spray), a nasal suspension, ointment, or gel (see page 3 lines 43-47). Typically the dosage units may be prepared to deliver 0.5mcg to about 100mcg of the glucocorticoid and 5mcg to about 1000mcg of the antihistamine spray (see page 3 lines 58 and page 4 lines 1-2). Example III discloses an intranasal pharmaceutical composition prepared by combining the following components utilizing conventional mixing techniques, shown below:

Component	Wgt %
triamcinolone acetonide	0.050
azelastine HCl	0.070
polysorbate 80	0.050
glycerin	2.000
hydroxypropyl methyl cellulose	1.000
sodium chloride	0.900
ethylenediamine tetraacetic acid	0.050
benzalkonium chloride	0.020
distilled water	q.s. to vol.

(see page 6, Example III).

Ascertainment of the difference between the prior art and the claims (MPEP 2141.02)

Cramer does not exemplify a nasal composition further comprising a propellant. This deficiency is cured by the teachings of Modi.

Modi teaches aerosol formulations for nasal delivery comprising pharmaceutical agents (i.e. anti-inflammatories, steroids, etc.), water, excipients and a propellant (see the abstract and column 3 lines 30-40). Improved penetration and absorption of the formulations can be achieved by mixing the formulation with propellants such as tetrafluroethane, etc., especially when delivered through aerosol devices (i.e. MDI). (see column 2 lines 5-24).

Finding of prima facie obviousness Rational and Motivation (MPEP 2142-2143)

One of ordinary skill in the art would have been motivated to make a composition further comprising a propellant because Modi suggests that adding propellants to nasal formulations can increase penetration and absorption in the nasal cavity.

Thus, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to make a composition further comprising a propellant for the purpose of increasing penetration of active formulations into the nasal cavity.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made because the prior art is fairly suggestive of the claimed invention.

16. Claims 1-3 and 6 are rejected under U.S.C. 103(a) as being unpatentable over Malmqvist-Granlund et al. (US 6,391,340).

Applicant claims a pharmaceutical formulation which comprises azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof and a steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, preferably the formulation being in a form suitable for nasal or ocular administration.

Determination of the scope and content of the prior art (MPEP 2141.01)

Malmqvist-Granlund et al. teach a dry powder solid particulate pharmaceutical formulation suitable for application to the nose comprising finely divided drug particles and a carrier, where at least 70% of the drug particles have a size below 15μm (see the abstract and column 1 lines 52-62). The drugs that are used are classes of drugs used to treat conditions of the nose such as antihistamines (i.e. azelastine) and anti-inflammatories (i.e. fluticasone) and mixtures thereof (see column 2 lines 36-40). Salts, hydrates, solvates and esters of the drugs can also be used (see column 2 lines 36-42).

Ascertainment of the difference between the prior art and the claims (MPEP 2141.02)

Malmqvist-Granlund et al. do not exemplify a dry powder composition comprising azelastine and a steroid with a particle size of less than 10μm.

Finding of prima facie obviousness Rational and Motivation (MPEP 2142-2143)

However, one of ordinary skill in the art would have been motivated to make a composition comprising azelastine and a steroid because Malmqvist-Granlund et al. suggest a dry powder formulation with a particle size of less than 15μm comprising a anti-inflammatory (i.e. fluticasone) and a antihistamine (i.e. azelastine), which will disperse evenly over the nasal mucosa.

Thus, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to make a composition comprising azelastine and a steroid

for the purpose of obtaining the benefits for the nose from such a combination and for increased delivery to the nasal mucosa.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made because the prior art is fairly suggestive of the claimed invention.

17. Claims 28-29 are rejected under U.S.C. 103(a) as being unpatentable over Cramer (EP 0780127) in view of Alfonso et al. (US 6,017,963).

Applicant claims a pharmaceutical formulation which comprises azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof and a steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, preferably the formulation being in a form suitable for nasal or ocular administration.

Determination of the scope and content of the prior art (MPEP 2141.01)

Cramer teaches a nasal spray composition comprising about 0.001 to about 0.2% concentration of a glucocorticosteroid (i.e. beclomethasone, flunisolide, triamcinolone, fluticasone, mometasone, bedusonide and pharmaceutically acceptable salts), 0.01 to about 4% concentration of an antihistamine (i.e. azelastine or pharmaceutically acceptable salt thereof, and an intranasal carrier (see the abstract and

page 2 lines 36-45). The composition may contain isotonic agents such as citric acid, boric acid, propylene glycol, etc., thickening agents such as xanthan gum, microcrystalline cellulose, carboxymethyl cellulose, hydroxypropyl cellulose, etc., humectants such as sorbitol, propylene glycol, polyethylene glycol, etc. and preservatives such as benzyl alcohol, phenylethyl alcohol, and quaternary ammoniums such as benzalkonium chloride (see page 4 lines 50-58 and page 5 lines 1-22). The pH of the composition is from about 4.5 to about 9 (see page 2 lines 57-58). The composition may be formulated into a nasal solution (for use as drops or a spray), a nasal suspension, ointment, or gel (see page 3 lines 43-47). Typically the dosage units may be prepared to deliver 0.5mcg to about 100mcg of the glucocorticoid and 5mcg to about 1000mcg of the antihistamine spray (see page 3 lines 58 and page 4 lines 1-2). Example III discloses an intranasal pharmaceutical composition prepared by combining the following components utilizing conventional mixing techniques, shown below:

Component	Wgt %
triamcinolone acetonide	0.050
azelastine HCl	0.070
polysorbate 80	0.050
glycerin	2.000
hydroxypropyl methyl cellulose	1.000
sodium chloride	0.900
ethylenediamine tetraacetic acid	0.050
benzalkonium chloride	0.020
distilled water	q.s. to vol.

(see page 6, Example III).

Ascertainment of the difference between the prior art and the claims (MPEP 2141.02)

Cramer does not exemplify a nasal composition further comprising a propellant. This deficiency is cured by the teachings of Alfonso et al.

Alfonso et al. teaches intranasal and/or inhalation administration of pharmaceutical agents (see the abstract). The dosage form suitable for intranasal and/or inhalation administration can be in the form of a liquid solution suspension, insufflation powder, etc. for administration as a nasal spray, drop or inhaled fine particles (i.e. insuflation) (see column 3 lines 1-65, column 5 lines 36-45, and column 7 lines 1-26).

Finding of prima facie obviousness Rational and Motivation (MPEP 2142-2143)

One of ordinary skill in the art would have been motivated to make the instant composition in the form of an insufflation powder because Alfonso et al. suggest the nasal compositions in the form of a spray, droplet, insufflation powder, etc.

Thus, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to make the instant composition in the form of an insufflation powder because it is an obvious variation of ways to administer a nasal composition as suggested Alfonso et al.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made because the prior art is fairly suggestive of the claimed invention.

Conclusion

18. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KRISTIE L. BROOKS whose telephone number is (571)272-9072. The examiner can normally be reached on M-F 8:30am-6:00pm Est..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann R. Richter can be reached on (571) 272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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

KB

/Mina Haghighatian/
Primary Examiner, Art Unit 1616

Notice of References Cited	Application/Control No. 10/518,016	Applicant(s)/Patent Under Reexamination LULLA ET AL.	
	Examiner KRISTIE L. BROOKS	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-6,391,340	05-2002	Malmqvist-Granlund et al.	424/489
*	B	US-6,294,153	09-2001	Modi, Pankaj	424/45
*	C	US-6,017,963	01-2000	Alfonso et al.	514/646
	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	EP 0780127	06-1997		Cramer	
	O					
	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.

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10518016	LULLA ET AL.
	Examiner	Art Unit
	KRISTIE L BROOKS	1616

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

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

CLAIM		DATE								
Final	Original	09/23/2008								
	1	✓								
	2	✓								
	3	✓								
	4	✓								
	5	✓								
	6	✓								
	7	✓								
	8	✓								
	9	✓								
	10	✓								
	11	✓								
	12	✓								
	13	✓								
	14	✓								
	15	✓								
	16	✓								
	17	✓								
	18	✓								
	19	✓								
	20	✓								
	21	✓								
	22	✓								
	23	N								
	24	N								
	25	✓								
	26	✓								
	27	✓								
	28	✓								
	29	✓								
	30	✓								
	31	✓								
	32	✓								
	33	✓								
	34	✓								
	35	✓								
	36	✓								

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10518016	LULLA ET AL.
	Examiner	Art Unit
	KRISTIE L BROOKS	1616

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

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

CLAIM		DATE								
Final	Original	09/23/2008								
	37	✓								
	38	✓								
	39	✓								
	40	✓								
	41	✓								
	42	✓								
	43	✓								
	44	✓								
	45	✓								
	46	N								
	47	N								
	48	N								
	49	N								
	50	N								

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10518016	LULLA ET AL.
	Examiner	Art Unit
	KRISTIE L BROOKS	1616

SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
Inventor Search	9/24/2008	KB
East Search	9/30/2008	KB

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

UNITED STATES PATENT AND TRADEMARK OFFICE

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

BIB DATA SHEET

CONFIRMATION NO. 4912

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
10/518,016	07/06/2005 RULE	514	1616	TPP31753

APPLICANTS

Amar Lulla, Mumbai, INDIA;
Geena Malhotra, Mumbai, INDIA;

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

This application is a 371 of PCT/GB03/02557 06/13/2003

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

UNITED KINGDOM 0213739.6 06/14/2002

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

Foreign Priority claimed ☑ Yes ☐ No 35 USC 119(a-d) conditions met ☑ Yes ☐ No Verified and Acknowledged /Kristie L. Brooks/ Examiner's Signature	☐ Met after Allowance KB Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		INDIA	0	51	3

ADDRESS

Novak, Druce & Quigg LLP
1300 I Street, N.W.
Suite 1000, West Tower
WASHINGTON, DC 20005
UNITED STATES

TITLE

Combination of azelastine and steroids

FILING FEE RECEIVED		
2580	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L79	799	(azelastine) fluticasone	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2008/09/30 16:33
L80	509	(azelastine) fluticasone (nasal)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2008/09/30 16:33
L81	332	(azelastine) fluticasone (nasal) (particle or particulate)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2008/09/30 16:34
L82	267	(azelastine) fluticasone (nasal) (particle or particulate) (micron or ".mu.m")	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2008/09/30 16:34
L83	189	(azelastine) fluticasone (nasal) ((particle or particulate) with (micron or ".mu.m"))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2008/09/30 16:34
L84	12	(azelastine).clm. fluticasone (nasal) ((particle or particulate) with (micron or ".mu.m"))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2008/09/30 16:34
L85	5	(azelastine).ab. fluticasone (nasal) ((particle or particulate) with (micron or ".mu.m"))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2008/09/30 16:35
L86	5	(azelastine) fluticasone (nasal).ti. ((particle or particulate) with (micron or ".mu.m"))	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2008/09/30 16:35
L87	148	(azelastine) fluticasone (nasal) ((particle or particulate) with (micron or ".mu.m")) spray	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2008/09/30 16:39

L88	171	(azelastine) fluticasone (nasal) ((particle or particulate) with size) spray	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2008/09/30 16:39
L89	40	(azelastine) fluticasone (nasal) ((particle or particulate) with size) spray (nasal with spray)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2008/09/30 16:39
L90	1	(azelastine) steriod (nasal) ((particle or particulate) with size) spray (nasal with spray)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2008/09/30 16:41
L91	61	(azelastine) steroid (nasal) ((particle or particulate) with size) spray (nasal with spray)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2008/09/30 16:41
L92	40	(azelastine) fluticasone (nasal) ((particle or particulate) with size) spray (nasal with spray)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2008/09/30 16:42
L93	171	(azelastine) fluticasone (nasal) ((particle or particulate) with size) spray	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2008/09/30 16:42
L94	1	(azelastine) fluticasone (nasal).ti. ((particle or particulate) with size) spray	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2008/09/30 16:42
L95	12	(azelastine) fluticasone (nasal).ab. ((particle or particulate) with size) spray	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2008/09/30 16:42
L96	171	(azelastine) fluticasone (nasal) ((particle or particulate) with size) spray	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2008/09/30 16:43
L97	138	(nasal).ti. ((particle or particulate) with size) spray	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2008/09/30 16:44

L98	33	(nasal).ti. ((particle or particulate) with size).ab. spray	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2008/09/30 16:44
L99	10	(nasal with spray).ti. ((particle or particulate) with size) spray	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2008/09/30 16:47
L100	197	(nasal with spray).clm. ((particle or particulate) with size) spray	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2008/09/30 16:49
L101	440	(nasal with spray) dry ((particle or particulate) with size) spray (antihistamine or anti-histamine or azelastine) (anti-inflammatory or antiinflammatory)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2008/09/30 16:50
L102	187	(nasal with spray) dry ((particle or particulate) with size) spray (antihistamine or anti-histamine or azelastine) (anti-inflammatory or antiinflammatory) rhinitis	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2008/09/30 16:51
L103	1178	(azelastine) (steroid or fluticasone or beclomethasone or flunisolide or triamcinolone or mometasone or budesonide)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2008/09/30 16:54
L104	701	(azelastine) (steroid or fluticasone or beclomethasone or flunisolide or triamcinolone or mometasone or budesonide) (nose or nasal)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2008/09/30 16:54
L105	7	(azelastine).ti. (steroid or fluticasone or beclomethasone or flunisolide or triamcinolone or mometasone or budesonide) (nose or nasal)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2008/09/30 16:54

L106	12	(azelastine) (steroid or fluticasone or beclomethasone or flunisolide or triamcinolone or mometasone or budesonide).ti. (nose or nasal)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2008/09/30 16:54
L107	168	(azelastine) (steroid or fluticasone or beclomethasone or flunisolide or triamcinolone or mometasone or budesonide).clm. (nose or nasal)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2008/09/30 17:00
L108	126	(azelastine) (steroid or fluticasone or beclomethasone or flunisolide or triamcinolone or mometasone or budesonide).clm. (nose or nasal) dry	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2008/09/30 17:00
L109	144	(azelastine) (steroid or fluticasone or beclomethasone or flunisolide or triamcinolone or mometasone or budesonide).clm. (nose or nasal or mucosal or intranasally or intraocular or ocular) dry	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2008/09/30 17:01
L110	385	(azelastine) fluticasone propellant	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2008/09/30 17:44
L111	263	(azelastine) fluticasone propellant (composition or formulation) (nose or nasal or mucosa)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2008/09/30 17:45
L112	383	(azelastine) fluticasone propellant (composition or formulation)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2008/09/30 17:49
L113	61	(azelastine) fluticasone.clm. propellant (composition or formulation)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2008/09/30 17:49

L114	104	nasal.ti. propellant (composition or formulation)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2008/09/30 18:03
L115	89	nasal.ti. propellant (composition or formulation) spray	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2008/09/30 18:03
L116	51	nasal.ti. propellant (composition or formulation) spray (azelastine or anti-inflammatory or antihistamine or anti-histamine or fluticasone)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2008/09/30 18:04
L117	3	insufflation poweder	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2008/09/30 18:29
L118	11116	insufflation powder	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2008/09/30 18:29
L119	6159	(insufflation with powder)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2008/09/30 18:29
L120	5170	(insufflation with powder) (nasal or nose or intranasal)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2008/09/30 18:30
L121	20	(insufflation with powder) (nasal or nose or intranasal).ti.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2008/09/30 18:30
L122	18	(insufflation with powder) (nasal or nose or intranasal).ti. (liquid or spray)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2008/09/30 18:30
L123	0	pressure.ti. packing.ti. MDI	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2008/09/30 18:55

L124	168	pressure.ti. MDI	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2008/09/30 18:56
L125	4	pressure.ti. MDI.ti.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2008/09/30 18:56
L126	67	azelastine.clm. fluticasone.clm.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	AND	ON	2008/09/30 19:03

9/30/2008 7:13:47 PM

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of

Amar LULLA et al

Group Art Unit: Unassigned

Serial No.: 10/518,016

Examiner: Unassigned

Filed: December 14, 2004

Confirmation No. 4912

For: COMBINATION OF AZELASTINE AND STEROIDS

INFORMATION DISCLOSURE STATEMENT

Commissioner of Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

Pursuant to Rules 56 and 98, Applicants hereby call the attention of the Patent Office to the references listed on the attached Form PTO 1449. These references were cited in an International Search Report issued in connection with the corresponding international application.

Applicants present these references so that the Patent Office may, in the first instance, determine any relevancy thereof to the presently claimed invention, see Beckman Instruments, Inc. v. Chemtronics, Inc., 439 F.2d 1369, 1380, 165 USPQ 355, 364 (5th Cir. 1970).

Applicants respectfully request that these references be expressly considered during the prosecution of this application and made of record herein and appear among the "References Cited" on any patent to issue herefrom.

Respectfully submitted,

TPP/mat
Attorney Docket No.: TPP 31753

Thomas P. Pavelko
Registration No. 31,689

STEVENS, DAVIS, MILLER & MOSHER, L.L.P.
1615 L Street, N.W., Suite 850
Washington, D.C. 20036
Telephone: (202) 785-0100
Facsimile: (202) 408-5200 or (202) 408-5088

Date: July 6, 2005

FORM PTO-1449 (Rev. 4/92) U.S. Department of Commerce Patent and Trademark Office	ATTY. DOCKET NO. TPP 31753	SERIAL NO. 10/518,016
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use several sheets if necessary)	APPLICANT Amar LULLA et al	
	FILING DATE December 14, 2004	GROUP Applications

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION	
							YES	NO
/K.B./		9 7 0 1 3 3 7	01/97	WO				
/K.B./		0 7 8 0 1 2 7	06/97	EP				

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

		Database Medline "Online! US National Library of Medicine (NLM), Bethesda, MD, US: 2000 Portmann D et al: "Acceptability of local treatment of allergic rhinitis with a combination of a corticoid (beclomethasone) and an antihistaminic (azelastine); vol. 121, no. 4, 2000, pages 273-279
		Busse W W et al: "Corticosteroid-Sparing Effect of Azelastine in the Management of Bronchial Asthma" - American Journal of Respiratory and Critical Care Medicine, American Lung Association, new York, NW, vol. 153, no. 1, 1996, pages 122-172, page 127, column 1, paragraph 2

EXAMINER	/Kristie Brooks/	DATE CONSIDERED	09/23/2008

EXAMINER: Initial if citation is considered, draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

(Form PTO-1449 [6-4])

JPW/1614

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of

Amar LULLA et al — Group Art Unit: 1614

Serial No.: 10/518,016 — Examiner: Unassigned

Filed: July 6, 2005 — Confirmation No. 4912

For: COMBINATION OF AZELASTINE AND STEROIDS

INFORMATION DISCLOSURE STATEMENT

Commissioner of Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

Pursuant to Rules 56 and 98, Applicants hereby call the attention of the Patent Office to the references listed on the attached Form PTO 1449. These references were cited in an International Search Report (copy enclosed) issued in connection with the corresponding international application.

Applicants present these references so that the Patent Office may, in the first instance, determine any relevancy thereof to the presently claimed invention, see Beckman Instruments, Inc. v. Chemtronics, Inc., 439 F.2d 1369, 1380, 165 USPQ 355, 364 (5th Cir. 1970).

Applicants respectfully request that these references be expressly considered during the prosecution of this application and made of record herein and appear among the "References Cited" on any patent to issue herefrom.

Respectfully submitted,

TPP/mtw
Attorney Docket No.: TPP 31753

Thomas P. Pavelko
Registration No. 31,689

STEVENS, DAVIS, MILLER & MOSHER, L.L.P.
1615 L Street, N.W., Suite 850
Washington, D.C. 20036
Telephone: (202) 785-0100
Facsimile: (202) 785-0100 or (202) 785-0200

Date: October 5, 2005

FORM PTO-1449 (Rev. 4/92) U.S. Department of Commerce Patent and Trademark Office

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use several sheets if necessary)

ATTY. DOCKET NO.	SERIAL NO.
TPP 31753	10/518,016
APPLICANT: Amar LULLA et al	
FILING DATE: July 6, 2005	GROUP: 1614

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
/K.B./		9701337	01/97	WO				
/K.B./		0780127	06/97	EP				
/K.B./		9848839	11/98	WO				
/K.B./	1	19947234	04/01	DE				

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

/K.B./		Database Medline "Online! US National Library of Medicine (NLM), Bethesda, MD, US: 2000 Portmann D et al: "Acceptability of local treatment of allergic rhinitis with a combination of a corticoid (beclomethasone) and an antihistaminic (azelastine); vol. 121, no. 4, 2000, pages 273-279
/K.B./		Busse W W et al: "Corticosteroid-Sparing Effect of Azelastine in the Management of Bronchial Asthma" - American Journal of Respiratory and Critical Care Medicine, American Lung Association, new York, NW, vol. 153, no. 1, 1996, pages 122-172, page 127, column 1, paragraph 2
/K.B./		International Search Report under Section 17 UK Patent Office collections, including GB, EP, WO & US patent specifications

EXAMINER /Kristie Brooks/ DATE CONSIDERED 09/23/2008

EXAMINER: Initial if citation is considered, draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

(Form PTO-1449 [6-4])

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NUMBER	PATENT NUMBER	GROUP ART UNIT	FILE WRAPPER LOCATION
10/518,016		1616	05P0

Correspondence Address / Fee Address Change

The following fields have been set to Customer Number 77176 on 02/25/2008

- Correspondence Address
- Maintenance Fee Address

The address of record for Customer Number 77176 is:
Novak, Druce & Quigg LLP
1300 I Street, N.W.
Suite 1000, West Tower
WASHINGTON,DC 20005

UNITED STATES PATENT AND TRADEMARK OFFICE

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

DATE: 08/11/2006

Davis Miller & Mosher
1615 L Street N W
Suite 850
Washington, DC 20036

To: Applicant of Serial Number 10518016
Filed on 06-JUL-2005
(Art Unit 1617)

It is estimated that this application will receive an Office action in approximately 23 months. This is an estimate that is based on the current inventory level of applications filed in this art area and the current staffing levels in this Art Unit. The USPTO is dedicated to minimizing first action and total pendency, and we are targeting resources to help address backlogs in art areas with high new application filings. Thank you for your inquiry.

Diane Williams

Customer Service Office in Technology Center: 1600

Phone Number: 571-272-1600
Central Fax Number: 571-273-8300

Applicant/Attorney Contact Information:

Phone Number: 202-785-0100
Fax Number:

IFW

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application

Amar LULLA et al — Group Art Unit: 1614

Serial No.: 10/518,016 — Examiner: Unassigned

Filed: July 6, 2005 — Confirmation No.: 4912

For: COMBINATION OF AZELASTINE AND STEROIDS

STATUS INQUIRY LETTER

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

Sir:

Kindly let us have the status of the above-identified application, including an indication as to when the next Office communication can be expected.

Respectfully submitted,

TPP/mat
Attorney Docket No.: TPP 31753

Thomas P. Pavelko
Registration No. 31,689

STEVENS, DAVIS, MILLER & MOSHER, L.L.P.
1615 L Street, N. W., Suite 850
Washington, D.C. 20036-5622
Telephone: (202) 785-0100
Facsimile: (202) 408-5200 or (202) 408-5088

Date: August 1, 2006

IFW

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application

Amar LULLA et al

Group Art Unit: 1614

Serial No.: 10/518,016

Examiner: Unassigned

Filed: July 6, 2005

Confirmation No.: 4912

For: COMBINATION OF AZELASTINE AND STEROIDS

STATUS INQUIRY LETTER

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

Sir:

Kindly let us have the status of the above-identified application, including an indication as to when the next Office communication can be expected.

Respectfully submitted,

TPP/mat
Attorney Docket No.: TPP 31753

Thomas P. Pavelko
Registration No. 31,689

STEVENS, DAVIS, MILLER & MOSHER, L.L.P.
1615 L Street, N. W., Suite 850
Washington, D.C. 20036-5622
Telephone: (202) 785-0100
Facsimile: (202) 408-5200 or (202) 408-5088

Date: February 7, 2006

JPW/1614

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of

Amar LULLA et al — Group Art Unit: 1614

Serial No.: 10/518,016 — Examiner: Unassigned

Filed: July 6, 2005 — Confirmation No. 4912

For: COMBINATION OF AZELASTINE AND STEROIDS

INFORMATION DISCLOSURE STATEMENT

Commissioner of Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

Pursuant to Rules 56 and 98, Applicants hereby call the attention of the Patent Office to the references listed on the attached Form PTO 1449. These references were cited in an International Search Report (copy enclosed) issued in connection with the corresponding international application.

Applicants present these references so that the Patent Office may, in the first instance, determine any relevancy thereof to the presently claimed invention, see Beckman Instruments, Inc. v. Chemtronics, Inc., 439 F.2d 1369, 1380, 165 USPQ 355, 364 (5th Cir. 1970).

Applicants respectfully request that these references be expressly considered during the prosecution of this application and made of record herein and appear among the "References Cited" on any patent to issue herefrom.

Respectfully submitted,

TPP/mtw
Attorney Docket No.: TPP 31753

Thomas P. Pavelko
Registration No. 31,689

STEVENS, DAVIS, MILLER & MOSHER, L.L.P.
1615 L Street, N.W., Suite 850
Washington, D.C. 20036
Telephone: (202) 785-0100
Facsimile: (202) 785-0100 or (202) 785-0200

Date: October 5, 2005

FORM PTO-1449 (Rev. 4/92) U.S. Department of Commerce Patent and Trademark Office

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use several sheets if necessary)

ATTY. DOCKET NO.	SERIAL NO.
TPP 31753	10/518,016
APPLICANT: Amar LULLA et al	
FILING DATE: July 6, 2005	GROUP: 1614

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
		9 7 0 1 3 3 7	01/97	WO				
		0 7 8 0 1 2 7	06/97	EP				
		9 8 4 8 8 3 9	11/98	WO				
	1	9 9 4 7 2 3 4	04/01	DE				

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

		Database Medline "Online! US National Library of Medicine (NLM), Bethesda, MD, US: 2000 Portmann D et al: "Acceptability of local treatment of allergic rhinitis with a combination of a corticoid (beclomethasone) and an antihistaminic (azelastine); vol. 121, no. 4, 2000, pages 273-279
		Busse W W et al: "Corticosteroid-Sparing Effect of Azelastine in the Management of Bronchial Asthma" - American Journal of Respiratory and Critical Care Medicine, American Lung Association, new York, NW, vol. 153, no. 1, 1996, pages 122-172, page 127, column 1, paragraph 2
		International Search Report under Section 17 UK Patent Office collections, including GB, EP, WO & US patent specifications

EXAMINER | DATE CONSIDERED

EXAMINER: Initial if citation is considered, draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

(Form PTO-1449 [6-4])

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61K 45/06, 31/57, 31/58, 31/135, 31/35, 31/245, 31/09, 31/38, 31/195, 31/47, 31/445, 31/55, 31/44, 31/615, 31/415

A1

(11) International Publication Number: **WO 98/48839**

(43) International Publication Date: 5 November 1998 (05.11.98)

(21) International Application Number: PCT/US98/06483

(22) International Filing Date: 2 April 1998 (02.04.98)

(30) Priority Data:
60/044,306 30 April 1997 (30.04.97) US

(71) Applicant *(for all designated States except US)*: WARNER-LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: SEGAL, Catherine, A. [US/US]; 60 Shawnee Avenue, Rockaway, NJ 07866 (US).

(74) Agents: RYAN, M., Andrea; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 (US) et al.

(81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CZ, EE, GE, GW, HU, ID, IL, IS, JP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, 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), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: TOPICAL NASAL ANTIINFLAMMATORY COMPOSITIONS

(57) Abstract

The present invention provides topically applicable nasal compositions comprising a therapeutically effective amount of an antiinflammatory agent and a therapeutically effective amount of at least one agent selected from the group consisting of a vasoconstrictor, a neuramidinase inhibitor, a leukotriene inhibitor, an antihistamine, an antiallergic agent, an anticholinergic agent, an anesthetic and a mucolytic agent. The present compositions are useful as nasal sprays and nose drops for the treatment of nasal and sinus conditions.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

TOPICAL NASAL ANTIINFLAMMATORY COMPOSITIONS

SPECIFICATION

BACKGROUND OF THE INVENTION

Topical nasal antiinflammatory preparations are known in the art for the treatment of inflammatory conditions of the nasal mucous membranes, and in particular for relief of the symptoms of nasal and sinus conditions such as rhinitis. However, nasal and sinus conditions may be characterized by diverse symptoms requiring treatment with multiple therapeutic agents. For example, allergic rhinitis may be characterized by rhinorrhea, nasal itching, sneezing, congestion and postnasal drip and treatment may require antihistamines, decongestants, antiallergics and anesthetics in addition to antiinflammatories.

The use of multiple topical nasal preparations to administer multiple therapeutic agents suffers from significant disadvantages. The volume of liquid that can effectively be applied nasally is limited by the surface area of the nostril and the bioadhesiveness of the liquid. In addition, a sufficient contact time between topical preparations and the surface area of the nostril is required to assure adequate dosing of a therapeutic agent. Further, spray formulations require a threshold surface tension to form droplets. Accordingly, the delivery volume per actuation is limited to the volume that will be retained in the nostril without premature drainage. Thus multiple topical nasal preparations cannot be effectively administered simultaneously.

Another disadvantage of the administration of multiple topical nasal preparations is patient inconvenience. Patient compliance may be compromised by the inconvenience of applying multiple spray products or nose drops. Patients complain when excess spray drains into their throats where it can be tasted, resulting in a need for flavor masking of bitter medicaments.

Accordingly, a need exists for a convenient means of nasal administration of multiple therapeutic agents.

SUMMARY OF THE INVENTION

The present invention provides topically applicable nasal compositions comprising a therapeutically effective amount of a topical antiinflammatory agent and a therapeutically effective amount of at least one agent suitable for topical nasal administration and selected from the group consisting of a vasoconstrictor, a neuramidinase inhibitor, an anticholinergic agent, a leukotriene inhibitor, an antihistamine, an antiallergic agent, an anesthetic, and a mucolytic agent.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides topically applicable nasal compositions comprising a topical antiinflammatory agent and at least one additional therapeutic agent. The present compositions are useful for the treatment of nasal and sinus conditions, for example allergic rhinitis or the common cold.

The topical antiinflammatory agents in the compositions of the present invention are corticosteroids known in the art to suppress inflammation. In a preferred embodiment the topical antiinflammatory agent is beclomethasone dipropionate, budesonide, dexamethasone, mometasone furoate, fluticasone proprionate or triamcinolone acetonide. The compositions contain a therapeutically effective amount of the selected antiinflammatory agent. Those of ordinary skill in the art can determine an amount that is therapeutically effective for the suppression of inflammation. The precise amount will depend upon the method of administration and the age, weight and condition of the subject to be treated. Generally the

antiinflammatory agents are utilized in dosages known in the art to be therapeutically effective upon nasal administration.

The compositions of the invention further comprise at least one additional therapeutic agent, and thus allow the convenient administration of an antiinflammatory agent and at least one additional therapeutic agent in a single topical nasal composition. The additional therapeutical agent is suitable for topical nasal administration and is selected from the group consisting of a vasoconstrictor, a neuramidinase inhibitor, a leukotriene inhibitor, an anticholinergic agent, an antihistamine, an antiallergic agent, a local anesthetic and a mucolytic agent. The use of an additional therapeutic agent in combination with an antiinflammatory agent provides additive and synergistic effects in the treatment of nasal and sinus conditions.

Vasoconstrictors suitable for topical nasal administration in the compositions of the present invention are oxymetazoline naphazoline, xylometazoline, and phenylephrine. Leukotriene inhibitors include zafirlukast, a selective, competitive receptor antagonist of the three leukotrienes C4, D4, and E4; pranlukast, a selective, competitive receptor antagonist of D4; and zileuton, a leukotriene inhibitor. A. neuramidinase inhibitor includes zanamivir (GG-167). Suitable antihistamines are diphenhydramine, chlorpheniramine, cetirizine terfenadine, fenofexadine, astemizole norastemizole, azelastine, and azatidine. Antiallergic agents include cromolyn sodium and nedocromil levocabastine. An anticholinergic agent useful in the compositions of the present invention is ipratropium bromide. Local topical anesthetics include dyclonine, pramoxine, and benzocaine. Mucolytic agents suitable for topical nasal administration are acetylcysteine, guaifenisin and mucocysteine. The therapeutically effect amount of foregoing agents can be determined by the ordinarily skilled artisan with regard to the known use of these agents in the art and taking into account the method of administration and the age, weight and condition of the subject to be treated.

The compositions of the present invention are formulated as aqueous solutions comprising an antiinflammatory agent and at least one additional therapeutic agent and further comprising a pharmaceutically acceptable nasal carrier.

The formulation of pharmaceutical compositions is generally known in the art and reference can be conveniently made to standard text such as Remington's Pharmaceutical Sciences, 1985, 17th ed., Mack Publishing Co., Easton, Pennsylvania.

Preferred nasal formulations are nose drops or nasal sprays containing a water buffered aqueous solution as a carrier. The compositions are preferably isotonic. Isotonic agents such as a sugars and sodium chloride are known in the art and may be included in the subject compositions.

The compositions of the present invention may also contain a humectant to increase viscosity and effect moisturization and ciliary vitality. Suitable humectants include glycerin, polyethylene glycol, propylene glycol and mixtures thereof.

Additional agents including pharmaceutically acceptable preservatives, stabilizers, flavoring agents, and pH adjusters are known in the art and may be included in the present compositions.

Another embodiment of the present invention provides preservative-free compositions comprising an anti-inflammatory agent and at least one additional therapeutic agent. Preservative-free compositions are preferred due to reduced sensitivity and increased patient acceptance. These can be prepared in unit dose or in systems which prevent contamination of the reservoir of solution.

The compositions of the present invention can be conveniently administered nasally to a human subject in dosage unit form to elicit the desired therapeutic effect of the antiinflammatory agent and the additional therapeutic agents described above. The compositions may be administered in the form of a nasal spray or nose drops. Nasal sprays may be provided as squeeze bottles or metered dose manual nasal spray pumps designed to deliver the desired dose in one or two sprays, for example. The composition may also be administered as aerosol spray formulations, for example as metered dose pressurized aerosols containing propellants such as halogenated hydrocarbons.

WHAT IS CLAIMED IS:

1. A topically applicable nasal composition comprising a therapeutically effective amount of a topical antiinflammatory agent and a therapeutically effective amount of at least one agent suitable for topical nasal administration and selected from the group consisting of a vasoconstrictor, a neuramidinase inhibitor, a leukotriene inhibitor, an antihistamine, an antiallergic agent, an cholinergic agent, an anesthetic and a mucolytic agent.

2. The composition of Claim 1 wherein said topical antiinflammatory agent is selected from the group consisting of beclomethasone diproprionate, budesonide, dexamethasone, mometasone furoate, fluticasone proprionate and triamcinolone acetonide.

3. The composition of Claim 1 wherein said vasoconstrictor is selected from the group consisting of oxymetazoline, naphazoline, xylometazoline, and phenylephrine.

4. The composition of Claim 1 wherein said antihistamine is selected from the group consisting of diphenhydramine, chlorpheniramine, terfenadine, azelastine, norastemizole, fexofenadine, cetirazine, astemizole and azatidine.

5. The composition of Claim 1 wherein said antiallergic agent is selected from the group consisting of cromolyn sodium, levocabastine, and nedocromil.

6. The composition of Claim 1 wherein said anticholinergic agent is ipratropium.

7. The composition of Claim 1 wherein said topical anesthetic is selected from the group consisting of dyclonine, pramosine, and benzocaine.

8. The composition of Claim 1 wherein said mucolytic agent is selected from the group consisting of acetylcysteine, guaifenesin and mucocysteine.

9. The composition of Claim 1 wherein said leukotriene inhibitor is selected from the group consisting of zafirlukast, pranlukah, and zileuton.

10. The composition of Claim 1 wherein said neuramidinace inhibitor is zanamivir.

11. A topically applicable nasal composition comprising a therapeutically effective amount of a topical antiinflammatory agent selected from the group consisting of beclomethasone diproprionate, budesonide, dexamethasone, mometasone furoate, fluticasone proprionate and triamcinolone acetonide and a therapeutically effective amount of at least one agent selected from the group consisting of oxymetazoline, phenylephrine, diphenhydramine, chlorpheniramine, terfenadine, astemizole, azatidine, cromolyn sodium, nedocromil, ipratropium bromide, dyclonine, benzocaine, acetylcysteine, guaifenesin and mucocysteine.

12. The composition of Claim 1 or 11 further comprising at least one humectant.

13. The composition of Claim 12 wherein said humectant is selected from the group consisting of glycerin, polyethylene glycol and propylene glycol.

14. The composition of Claim 1 or 11 comprising a pharmaceutically acceptable carrier.

15. The composition of Claim 1 or 11 formulated for application as a nasal spray.

16. The composition of Claim 1 or 11 formulated for application as nose drops.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/06483

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K45/06 A61K31/57 A61K31/58 A61K31/135 A61K31/35
A61K31/245 A61K31/09 A61K31/38 A61K31/195 A61K31/47
A61K31/445 A61K31/55 A61K31/44 A61K31/615 A61K31/415

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.
X	WO 97 01337 A (MCNEIL-PPC, INC.) 16 January 1997 see abstract see page 2, line 8 - line 18 see page 8, line 2 - line 24	1,2,4, 11-16
X	WO 97 01341 A (MCNEIL-PPC, INC.) 16 January 1997 see page 2, line 5 - line 14 see page 8, line 2 - line 19	1,2,5, 11-16
X	WO 93 09764 A (CENTER FOR INNOVATIVE TECHNOLOGY) 27 May 1993 see page 6, line 10 - line 14 see page 6, line 30 see page 22, line 23 - line 33 see page 26, line 23 - line 25 see claims 1,2,4-8,13-23	1,3,4,6, 14-16

-/--

[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
11 June 1998	22/06/1998

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	Alvarez Alvarez, C

1

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/06483

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE WPI Week 8733 Derwent Publications Ltd., London, GB; AN 87-230755 XP002067758 & JP 62 153 227 A (SEKISUI CHEM. IND. CO. LTD.) , 8 July 1987 see abstract	1,2,4,7
X	WO 95 07103 A (THE PROCTER & GAMBLE COMPANY) 16 March 1995 see abstract see page 4, line 7 - line 13 see page 5, line 11 - line 31 see page 7, line 16 - line 18 see page 7, line 20 see examples 1-5	1,3,4,8, 12-14
A		7
X	US 3 482 015 A (FREDERICK W. BOLLINGER ET AL.) 2 December 1969 see the whole document	1-3,11, 12,14,15
X	WO 85 04589 A (SUNSHINE ET AL.) 24 October 1985 see claims 1,14,15,17-19	1,3,4,8, 14
X	WO 97 09067 A (BAYER AG. ET AL) 13 March 1997 see claims 1,5	1,2
A		9
X	US 4 053 628 A (NEIL ARTHUR STEVENSON ET AL.) 11 October 1977 see column 3, line 10 - line 18 see claim 2	1,5
X,P	EP 0 780 127 A (THE PROCTER & GAMBLE COMPANY) 25 June 1997 see page 2, line 35 - line 46 see page 3, line 14 - line 30 see page 4, line 5 - line 32 see page 4, line 38 - line 40 see page 5, line 7 - line 9 see claims 1-6	1-5,8, 11-16

1

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/06483

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9701337 A	16-01-1997	AU 6392496 A	30-01-1997
WO 9701341 A	16-01-1997	AU 6290396 A	30-01-1997
WO 9309764 A	27-05-1993	US 5240694 A	31-08-1993
		CA 2122719 A	27-05-1993
		EP 0661967 A	12-07-1995
		JP 8508007 T	27-08-1996
		US 5422097 A	06-06-1995
		US 5492689 A	20-02-1996
WO 9507103 A	16-03-1995	AU 7604094 A	27-03-1995
		BR 9407414 A	12-11-1996
		CA 2170488 A	16-03-1995
		CN 1130354 A	04-09-1996
		EP 0719156 A	03-07-1996
		JP 9502201 T	04-03-1997
US 3482015 A	02-12-1969	DE 1617610 A	20-04-1972
		FR 1481087 A	09-08-1967
		GB 1089043 A	
		NL 6601472 A	09-08-1966
WO 8504589 A	24-10-1985	US 4552899 A	12-11-1985
		AU 2029195 A	03-08-1995
		AU 589554 B	19-10-1989
		AU 4120085 A	01-11-1985
		CA 1258430 A	15-08-1989
		DE 3585495 A	09-04-1992
		EP 0180597 A	14-05-1986
		JP 61501913 T	04-09-1986
		US 4749697 A	07-06-1988
		US 4839354 A	13-06-1989
		US 4749722 A	07-06-1988
		US 4749711 A	07-06-1988
		US 4749723 A	07-06-1988
		US 4749720 A	07-06-1988
		US 4749721 A	07-06-1988
		US 4783465 A	08-11-1988
		US 4920149 A	24-04-1990

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/06483

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 8504589 A		US 4840962 A	20-06-1989
		US 4871733 A	03-10-1989
		US 5025019 A	18-06-1991
		US 4619934 A	28-10-1986
		US 4738966 A	19-04-1988
WO 9709067 A	13-03-1997	DE 19532714 A	06-03-1997
		AU 6984496 A	27-03-1997
US 4053628 A	11-10-1977	GB 1473318 A	11-05-1977
		GB 1399834 A	02-07-1975
		US 3975536 A	17-08-1976
		AU 465305 B	25-09-1975
		AU 4208072 A	15-11-1973
		BE 782981 A	03-11-1972
		CA 1000201 A	23-11-1976
		CY 955 A	22-12-1978
		DE 2223237 A	14-12-1972
		DE 2266025 A	07-03-1985
		DK 131324 B	30-06-1975
		FR 2139872 A	12-01-1973
		HK 69276 A	12-11-1976
		NL 7206251 A,B	14-11-1972
		SE 396011 B	05-09-1977
		ZA 7202823 A	28-03-1973
		DE 2425281 A	19-12-1974
		FR 2230358 A	20-12-1974
		JP 1160498 C	10-08-1983
		JP 50040720 A	14-04-1975
		JP 57056448 B	30-11-1982
EP 780127 A	25-06-1997	NONE	

PN - DE19947234 A 20010405

PD - 2001-04-05

PR - DE19991047234 19990930

OPD - 1999-09-30

AB - The invention relates to a novel combination of a soft steroid, especially loteprednol, and at least one antihistamine such as e.g., azelastine and/or levocabastine, for simultaneous, sequential or separate application for the local treatment of allergies and respiratory tract diseases, e.g., allergic rhinitis (rhinoconjunctivitis).

IN - ENGEL JUERGEN (DE);HEER SABINE (DE);MARX DEGENHARD (DE); SZELENYI ISTVAN (DE)

PA - ASTA MEDICA AG (DE)

IC - A61K31/56 ; A61P11/00

TI - Drug combination of soft steroid, preferably loteprednol, and antihistamine, administered by inhalation for effective treatment of respiratory or allergic diseases, e.g. allergic rhinitis

PR - DE19991047234 19990930

PN - CZ200201014 A3 20020612 DW200251 A61K31/56 000pp
- DE19947234 A1 20010405 DW200129 A61K31/56 006pp
- WO0122955 A2 20010405 DW200129 A61K31/00 Ger 000pp
- AU200079073 A 20010430 DW200142 A61K31/00 000pp
- BR200014312 A 20020521 DW200238 A61K31/00 000pp
- EP1216046 A2 20020626 DW200249 A61K31/56 Ger 000pp

PA - (ASTA) ASTA MEDICA AG
- (VIAT-N) VIATRIS GMBH & CO KG

IC - A61K31/00 ;A61K31/56 ;A61K45/08 ;A61P11/00 ;A61P11/02

IN - ENGEL J; HEER S; MARX D; SZELENYI I

AB - DE19947234 NOVELTY - A novel mixture contains (A) a 'soft' steroid and or its ester and (B) at least one antihistamine (preferably an antihistamine suitable for topical administration), in fixed or free combination.
- DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for:
- (1) a medicament for the treatment disease of the lower and/or upper respiratory tract and/or treatment of allergies, comprising (A) and (B) (suitable for topical administration) in free or fixed combination, optionally together with conventional auxiliaries or

carriers; and

- (2) preparation of medicaments as in (i) by mixing and formulating the appropriate components.
- ACTIVITY - Antiallergic; antiinflammatory; ophthalmological.
- In tests for the inhibition of Ascaris suum extract-induced rhinorrhea in sensitized guinea pigs by intranasal administration, loteprednol at 20 mu g gave 8% inhibition of nasal secretion, azelastine at 10 mu g alone gave 15% inhibition and a combination of 20 mu g loteprednol and 10 mu g formoterol gave 48% inhibition.
- MECHANISM OF ACTION - Tumor necrosis factor- alpha release inhibitor.
- USE - For treating respiratory tract diseases and/or allergies, specifically allergic rhinitis, rhinoconjunctivitis or rhinorrhea (claimed).
- ADVANTAGE - The (A)/(B) combinations are highly effective at low doses when administered topically. The low doses minimize side-effects and improve patient compliance. (B) rapidly alleviates the acute symptoms of allergy (e.g. redness, running nose, itching and swelling) and (A) combats the underlying inflammation. The (A)/(B) combinations are markedly more effective than either agent alone in inhibiting lipopolysaccharide-induced tumor necrosis factor- alpha release from diluted human blood and in inhibiting Ascaris suum extract-induced rhinorrhea in sensitized guinea pigs.
- (Dwg.0/0)

OPD - 1999-09-30

DN - AU BG BR BY CA CN CZ DZ EE GE HR HU ID IL IN IS JP KG KR KZ LT LV MK MX NO NZ PL RO RU SG SI SK TR UA US UZ YU ZA

DS - AT BE CH CY DE DK EA ES FI FR GB GR IE IT LU MC NL PT SE LI

AN - 2001-274582 [29]

(19) BUNDESREPUBLIK DEUTSCHLAND

DEUTSCHES PATENT- UND MARKENAMT

(12) **Offenlegungsschrift**

(10) **DE 199 47 234 A 1**

(51) Int. Cl.[7]:
A 61 K 31/56
A 61 P 11/00

(21) Aktenzeichen: 199 47 234.3
(22) Anmeldetag: 30. 9. 1999
(43) Offenlegungstag: 5. 4. 2001

DE 199 47 234 A 1

(71) Anmelder:
ASTA MEDICA AG, 01277 Dresden, DE

(72) Erfinder:
Szelenyi, Istvan, Prof., 90571 Schwaig, DE; Marx, Degenhard, Dr., 01445 Radebeul, DE; Heer, Sabine, 01445 Radebeul, DE; Engel, Jürgen, Prof., 63755 Alzenau, DE

Die folgenden Angaben sind den vom Anmelder eingereichten Unterlagen entnommen

(54) Neue Kombination von Loteprednol und Antihistaminika

(57) Die vorliegende Erfindung betrifft eine neue Kombination von einem Soft-Steroid, insbesondere Loteprednol, und mindestens einem Antihistaminikum, wie z. B. Azelastin und/oder Levocabastin, für die simultane, sequentielle oder separate Applikation bei der lokalen Behandlung von Allergien und Atemwegserkrankungen, beispielsweise der allergischen Rhinitis (Rhinokonjunktivitis).

DE 199 47 234 A 1

BUNDESDRUCKEREI 02.01 102 014/775/1

Beschreibung

Die vorliegende Erfindung betrifft eine neue Kombination von einem Soft-Steroid, insbesondere Loteprednol, und mindestens einem Antihistaminikum, wie z. B. Azelastin und/oder Levocabastin, für die simultane, sequentielle oder separate Applikation bei der lokalen Behandlung von Allergien und Atemwegserkrankungen, beispielsweise der allergischen Rhinitis (Rhinokonjunktivitis).

Hintergrund der Erfindung

Weltweit nimmt die Anzahl der allergischen Erkrankungen stark zu. Studien haben ergeben, daß weltweit durchschnittlich 7,5% aller Kinder und Jugendlichen an Rhinokonjunktivitis (Heuschnupfen kombiniert mit einer Augensymptomatik) leiden (Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis and atopic eczema: ISAAC, Lancet, 351, 1225–1332, 1998). In westeuropäischen Ländern ist die Prävalenz mit ca. 14% deulich höher (Annesi-Maesano I. and Oryszczyn MP.: Rhinitis in adolescents, Results of the ISAAC survey, Revue Francaise d'Allergologie et d'Immunologie Clinique, 38, 283–289, 1998; Norrman E., Nystrom L., Jonsson E and Stjernberg N: Prevalence and incidence of asthma and rhinoconjunctivitis in Swedish teenagers, European Journal of Allergy and Clinical Immunology, 53, 28–35, 1998). Trotz intensiver Forschungsaktivitäten ist die Pathogenese der Rhinokonjunktivitis immer noch nicht vollständig geklärt. Auch wenn in den vergangenen Jahren deutliche Fortschritte in der medikamentösen Behandlung dieser Erkrankung erzielt wurden, ist die Therapie immer noch nicht zufriedenstellend. Die akuten Symptome (Juckreiz, Rötung, Schwellung, Nasen- bzw. Tränenfluß) der Rhinokonjunktivitis können u. a. mit Hilfe von Antihistaminika gut beherrscht werden. Jedoch haben sie kaum einen therapeutisch relevanten Einfluß auf die der Erkrankung zugrunde liegende und stets fortschreitende Entzündung. Oft wird die allergische Rhinitis (Rhinokonjunktivitis) sowohl von Patienten als auch vom Arzt als eine Bagatellerkrankung angesehen und dementsprechend nur unzureichend behandelt. In der Folge kann es jedoch zu einem sog. Etagenwechsel kommen, d. h. aus der relativ harmlosen Rhinitis entwickelt sich eine sehr ernst zu nehmendes Asthma bronchiale. Aus diesem Grunde ist es unerläßlich, bereits die allergische Rhinokonjunktivitis ausreichend und intensiv zu behandeln. Nur dann können die Patienten beschwerdefrei leben und nur dann kann ein u. U. lebensbedrohlicher Etagenwechsel verhindert werden.

Häufig ist es für den behandelnden Arzt in Grenzfällen nicht mit letzter Sicherheit festzustellen, ob noch "nur" eine Rhinokonjunktivitis oder bereits eine Atemwegserkrankung, wie Asthma bronchiale, vorliegt. Vorteilhaft ist, daß die erfindungsgemäße Kombination auch zur Behandlung von Erkrankungen der oberen und unteren Atemwege eingesetzt werden kann.

Zum gegenwärtigen Zeitpunkt können die Corticosteroide die der Rhinokonjunktivitis zugrunde liegende Entzündung am wirksamsten bekämpfen. Viele Patienten aber auch Ärzte setzen jedoch diese Medikamente wegen ihrer möglichen systemischen Nebenwirkungen (z. B. Wachstumsverlangsamung, Osteoporose) überhaupt nicht oder nur sehr zögernd, meistens erst in einer späten Phase der Erkrankung ein. Loteprednol gehört zu den sog. "soft" Steroiden. Im Gegensatz zu anderen Corticosteroiden, die meistens erst in der Leber zu pharmakodynamisch inaktiven Metaboliten abgebaut werden, erfolgt bei den "soft" Steroiden die metabolische Inaktivierung zum Teil bereits an der Stelle ihrer Verabreichung (intranasal, oculär oder intrapulmonal). Infolge dieser partiellen lokalen Metabolisierung gelangt keine oder nur sehr wenige pharmakodynamisch aktive Substanz in den systemischen Blutkreislauf, so daß praktisch mit den steroidspezifischen Nebenwirkungen nicht zu rechnen ist. Loteprednol ist für die Therapie der allergischen Konjunktivitis und Uveitis bereits zugelassen.

Antihistaminika werden in der akuten Phase der allergischen Rhinokonjunktivitis zur Linderung der oft quälenden Symptome eingesetzt. Besonders vorteilhaft ist die topische Applikation dieser Medikamente, da dadurch hohe lokale Konzentrationen vom Wirkstoff aufgebaut werden können ohne mit nennenswerten Nebenwirkungen rechnen zu müssen. Zum gegenwärtigen Zeitpunkt befinden sich zwei lokal verabreichbare Antihistaminika, Azelastin und Levocabastin auf dem Markt. Beide sind hochwirksam und sehr gut verträglich.

Überraschenderweise wurde nun gefunden, daß die neue Kombination von einem Soft-Steroid und mindestens einem Antihistaminikum bei der Behandlung von Allergien und/oder Atemwegserkrankungen durch topische Verabreichung vorteilhaft ist. Die Verabreichung kann dabei simultan, sequentiell oder separat erfolgen. Die Erfindung dient der Verbesserung der Therapie von allergischer Rhinitis (Rhinokonjunktivitis). Das Antihistaminikum sorgt für die schnelle Beseitigung der akuten Symptome (z. B. Rötung, Juckreiz, Schwellung). Mit dem in der Kombination enthaltenen Corticosteroid kann die dem Krankheitsbild zugrunde liegenden Entzündung erfolgreich bekämpft werden.

Gemäß einer Ausführungsform der Erfindung ist Loteprednol und dessen pharmazeutisch annehmbare Ester, insbesondere Loteprednol Etabonat ein besonders geeignetes Soft-Steroid. Die Herstellung von Loteprednol und Loteprednol Etabonat ist beispielsweise in dem deutschen Patent Nr. DE 31 26 732, dem korrespondierenden U.S.-Patent Nr. 4,996,335 und dem korrespondierenden japanischen Patent Nr. JP-89 011 037 beschrieben.

Weitere erfindungsgemäß geeignete Soft-Steroide sind beispielsweise in dem deutschen Patent Nr. 37 86 174, dem korrespondierenden europäischen Patent Nr. EP 0 334 853 sowie dem korrespondierenden U.S.-Patent Nr. 4,710,495 beschrieben.

Azelastin und Levocabastin können auch in Form der pharmazeutisch verträglichen Salze verwendet werden. Bevorzugt sind beispielsweise die Hydrochloride.

Durch die topische Verabreichung der Komponenten (Steroid und Antihistaminikum) können therapeutisch wirksame Konzentrationen bereits bei niedrigen Dosierungen erreicht werden. Die kombinative Gabe beider Substanzen (Antihistaminikum + Loteprednol) ermöglicht die Bekämpfung der lästigen Frühphasenreaktionen wie Juckreiz, Nasenfluß durch das Antihistaminikum und das Fortschreiten der Entzündung durch das Loteprednol. Außerdem wird dadurch die Gefahr des Auftretens von unerwünschten Wirkungen auf ein Minimum reduziert und somit ist eine bessere Compliance der Patienten zu erwarten.

Die vorliegende Erfindung beschreibt eine neue Kombination, in der ein Soft-Steroid (vorzugsweise Loteprednol) und

ein Antihistaminikum (vorzugsweise Azelastin und/oder Levocabastin) gleichzeitig, hintereinander als Einzelsubstanzen oder als fixe Kombination topisch (intranasal oder intraocular) gegeben werden. Durch diese Kombination kommt es nicht nur zu einem schnellen Wirkungseintritt, sondern auch zu einer hohen therapeutischen Wirksamkeit, die mit einer starken antientzündlichen Wirkung einhergeht. In einer vorteilhaften Ausführungsform liegen die wirksamen Komponente dieser Kombination in Form einer fixen Kombination vor, wodurch die Anwendung für den Patienten einfacher ist, denn beide Wirkstoffe sind in ein und demselben Behälter enthalten.

Gemäß einer weiteren Ausführungsform der Erfindung kann das Antihistaminikum auch oral verabreicht werden.

Die vorgesehene Dosierung erfolgt zweimal täglich, wobei die Einzeldosis vom "soft" Steroid (Loteprednol) zwischen 10 und 500 µg, bevorzugt 50 und 200 µg, liegt. Die Dosis vom Antihistaminikum beträgt 50–500 µg, bevorzugt 100–200 µg. Die tatsächliche Dosis hängt vom allgemeinen Zustand der Patienten (Alter, Gewicht, etc.) und Schweregrad der Erkrankung ab.

Folgende pharmakologische Untersuchung wurde durchgeführt um die beschriebene Erfindung zu untermauern.

In vitro wurden Untersuchungen zur Beeinflussung der Freisetzung des proinflammatorischen Cytokins TNFα im 1 : 5 verdünnten Humanblut verschiedener Spender durchgeführt. Die Stimulation erfolgte mit Lipopolysaccharid (LPS) von Salmonella abortus equi (10 µg/ml) über 24 h bei 37°C und 5% CO_2 im Brutschrank. Die Bestimmung der TNFα-Freisetzung erfolgte mit einem ELISA, aufgebaut aus Antikörpern der Fa. Pharmingen. Die Ergebnisse wurden als prozentuale Hemmung der LPS-induzierten TNFα-Freisetzung angegeben und sind in der Tabelle 1 dargestellt.

Tabelle 1

Wirkstoff	Konzentration [µmol/l]	Hemmung der TNFα-Freisetzung
Azelastin	10	2 %
Loteprednol	0,001	1 %
	0,01	2 %
	0,03	8 %
Azelastin + Loteprednol	10 + 0,001	12 %*
	10 + 0,01	18 %*
	10 + 0,03	22 %*

* signifikant ($p<0.05$)

Werden das Antihistaminikum Azelastin oder das "soft" Steroid Loteprednol allein appliziert, bleibt die LPS-induzierte TNFα-Freisetzung praktisch unverändert. In der Anwesenheit von Azelastin (10 µmol/l) wird die TNFα-Freisetzung durch Loteprednol konzentrationsabhängig verstärkt gehemmt.

In vivo Untersuchungen wurden an jungen, mit einem Antigen (Extrakt aus Ascaris suum) aktiv sensibilisierten Hausschweinen durchgeführt. Drei Wochen später wurden sie einer Allergen-Provokation ausgesetzt, die durch intranasale Instillation des Ascaris-Extraktes erfolgte. Diese lokale intranasale Allergen-Provoaktion führt zu einem sehr starken Anstieg der nasalen Sekretion (Rhinorrhoe). Die Sekretmenge wurde gravimetrisch erfaßt. Die Ergebnisse sind in der Tabelle 2 zusammengestellt.

Tabelle 2

Wirkstoff	Dosis in µg/Nasenloch	Hemmung der nasalen Sekretion	Anzahl der Tiere
Azelastin	10	15 %	5
Loteprednol	20	8 %	5
Azelastin + Loteprednol	10 + 20	48 %*	5

* signifikant ($p<0.05$)

Wenn das Antihistaminikum Azelastin oder das "soff" Steroid Loteprednol bei den Dosierungen 10 bzw. 20 µg/Nasenloch verwendet wird, kommt es nur zu marginalen Hemmungen der allergisch induzierten nasalen Hypersekretion. Wenn beide Wirkstoffe aber gleichzeitig gegeben werden, wird die Rhinorrhoe um 48% (signifikant) reduziert.

Für die topische Anwendung können verschiedene pharmazeutische Formulierungen, z. B. Nasensprays, Nasentropfen und Augentropfen, in Frage kommen.

Die vorliegende Erfindung beschreibt eine Kombination, in der ein Soft-Steroid, z. B. Loteprednol, und ein Antihistaminikum, z. B. Azelastin und/oder Levocabastin, gleichzeitig, als Einzelsubstanzen hintereinander oder als fixe Kombination verabreicht werden.

Aufgrund der Wasserlöslichkeit des Wirkstoffes Azelastinhydrochlorid können Formulierungen mit diesem Wirkstoff vorzugsweise als Lösungen formuliert werden. Loteprednoletabonat ist dagegen praktisch wasserunlöslich und wird daher als wässrige Suspension formuliert. In einer Formulierung in der beide Wirkstoffe kombiniert werden, liegt demnach Azelastinhydrochlorid in Wasser gelöst und Loteprednoletabonat in Wasser suspendiert vor.

Neben den wirksamen Bestandteilen Antihistaminikum, z. B. Azelastinhydrochlorid, und Soft-Steroid, z. B. Loteprednoletabonat, können die erfindungsgemäßen pharmazeutischen Zubereitungen weitere Bestandteile wie Konservierungsstoffe, Stabilisatoren, Isotonisierungsmittel, Verdickungsmittel, Suspensionsstabilisatoren, Hilfstoffe zur pH-Wert-Einstellung, Puffersysteme und Netzmittel enthalten.

Zum Beispiel kommen als Konservierungsmittel in Frage: Benzalkoniumchlorid, Chlorbutanol, Thiomersal, Methylparaben, Propylparaben, Sorbinsäure und deren Salze, Natriumedetat, Phenylethylalkohol, Chlohexidinhydrochlorid-acetat, -digluconat, Cetylpyridiniumchlorid, -bromid, Chlokresol, Phenylquecksilberacetat, Phenylquecksilbernitrat, Phenyquecksilberborat, Phenoxyethanol.

Für die Konservierung wird vorzugsweise eine Kombination aus Natriumedetat und Benzalkoniumchlorid verwendet. Natriumedetat wird dabei in Konzentrationen von 0,05–0,1% und Benzalkoniumchlorid in Konzentrationen von 0,005–0,05 eingesetzt. Auch eine Kombination aus Natriumedetat, Benzalkoniumchlorid und Phenylethylalkohol wird bevorzugt eingesetzt.

Geeignete Hilfsstoffe zur Einstellung der Isotonie der Formulierungen sind beispielsweise: Natriumchlorid, Kaliumchlorid, Mannitol, Glucose, Sorbitol, Glycerol, Propylenglycol. Im Allgemeinen werden diese Hilfsstoffe in Konzentrationen von 0,1 bis 10% eingesetzt.

Die Formulierungen der Erfindung können ebenfalls geeignete Puffersysteme oder andere Hilfsstoffe zur pH-Einstellung beinhalten um einen pH-Wert einzustellen und aufrechtzuerhalten in der Größenordnung von 4–8, vorzugsweise von 5 bis 7,5. Geeignete Puffersysteme sind Citrat, Phosphat, Tromethamol, Glycin, Borat, Acetat. Diese Puffersysteme können hergestellt werden aus Substanzen wie, Citronensäure, Mononatriumphosphat, Dinatriumphosphat, Glycin, Borsäure, Natriumtertaborat, Essigsäure, Natriumactat.

Es können ebenfalls weitere Hilfsstoffe zur pH-Einstellung verwendet werden wie Salzsäure oder Natriumhydroxid.

Um eine stabile wässrige Suspension mit dem wasserunlöslichen Wirkstoff Loteprednoletabonat herzustellen sind weiterhin geeignete Suspensionsstabilisatoren sowie geeignete Netzmittel erforderlich, um den suspendierten Wirkstoff in geeigneter Weise zu dispergieren und zu stabilisieren.

Als Suspensionstabilisatoren kommen wasserlösliche oder teilweise wasserlösliche Polymere in Frage: dazu gehören beispielsweise Methylcellulose (MC), Natriumcarboxymethylcellulose (Na-CMC), Hydroxypropylmethylcellulose (HPMC) Polyvinylalkohol (PVAL), Polyvinypyrrolidon (PVP), Polyacrylsäure, Polyacrylamid, Gellan Gum (Gelrite®) Aluminiumoxydhydrat (Unemul®) Dextrine, Cyclodextrine sowie Mischungen aus Mikrokristalliner Cellulose und Natriumcarboxymethylcellulose (Avicel RC 501®, Avicel RC 581®, Avicel RC 591®, Avicel CL 611®).

Diese Substanzen können gleichzeitig als Verdickungsmittel dienen um die Viskosität zu erhöhen und dadurch den Kontakt der Wirkstoffe mit dem Gewebe am Applikationsort zu verlängern.

Als Netzmittel für die Formulierungen kommen in Frage: Benzalkoniumchlorid, Cetylpyridiniumchlorid, Tyloxapol,

verschiedene Polysorbate (Tween®) sowie weitere polyoxyethylierte Substanzen und Poloxamere.

Beispiele

Die nachfolgenden Beispiele illustrieren die Erfindung ohne diese zu beschränken.

Beispiel 1

Nasenspray mit Azelastinhydrochlorid (0,1%)

Azelastinhydrochlorid	0,1000 g
Hydroxypropylmethylcellulose	0,1000 g
Natriumedetat	0,0500 g
Benzalkoniumchlorid	0,0125 g
Natriumhydoxid	q.s. ph 6,0
Sorbitol Lösung 70%	6,6666 g
Gereinigtes Wasser	ad 100 ml

Herstellung der Lösung

In einem geeigneten Rührwerksbehälter ca. 45 kg gereinigtes Wasser vorlegen. Darin den Wirkstoff, Hydroxypropylmethylcellulose, Natriumedetat, Benzalkoniumchlorid und Sorbitollösung nacheinander zugeben und unter Rühren auflösen. Die entstandene Lösung mit gereinigtem Wasser auf ein Volumen von 49,5 Liter auffüllen. Den pH-Wert der Lösung mit 1 N Natronlauge auf pH 6,0 einstellen. Mit gereinigtem Wasser auf das Endvolumen von 50,0 Liter auffüllen und Rühren. Die Lösung durch ein geignetes Filter filtrieren und in Flaschen abfüllen, welche anschließend mit einer geeigneten Nasenspraypumpe versehen werden.

Beispiel 2

Nasenspray-Suspension mit Loteprednoletabonat (1%)

Loteprednoletabonat	1,0000 g
Avicel RC 591	1,1000 g
Polysorbat 80	0,1000 g
Sorbitol-lösung 70%	6,0000 g
Natriumedetat	0,0500 g
Benzalkoniumchlorid	0,0200 g
Gereinigtes Wasser	ad 100 ml

Herstellung

In einem geeigneten Rührwerksbehälter mit Homogenisiereinrichtung 45 kg gereinigtes Wasser vorlegen und darin Avicel RC 591 hochtourig einhomogenisieren. Danach nacheinander die Stoffe Polysorbat 80, Sorbitol-Lösung, Natriumedetat und Benzalkoniumchlorid unter Rühren auflösen.

Anschließend den Wirkstoff Loteprednoletabonat hochtourig einhomogenisieren, bis eine gleichmäßige Suspension entstanden ist. Danach auf das Endvolumen von 50 Liter mit gereinigtem Wasser auffüllen und weiter homogenisieren. Anschließend die Suspension evakuieren um die entstandenen Luftblasen zu entfernen. Die entstandene Suspension wird anschließend in Flaschen abgefüllt, welche danach mit einer geeigneten Nasenspraypumpe versehen werden.

Beispiel 3

Nasenspray mit Loteprednoletabonat (1%, suspendiert) und Azelastinhydrochlorid (0,1%, gelöst)

Loteprednoletabonat	1,0000 g
Azelastinhydrochlorid	0,1000 g
Avicel RC 591	1,1000 g
Polysorbat 80	0,1000 g
Sorbitol-lösung 70%	6,0000 g
Natriumedetat	0,0500 g
Benzalkoniumchlorid	0,0200 g
Gereinigtes Wasser	ad 100 ml

Herstellung

In einem geeigneten Rührwerksbehälter mit Homogenisiereinrichtung 45 kg gereinigtes Wasser vorlegen und darin Avicel RC 591 hochtourig einhomogenisieren. Danach nacheinander den Wirkstoff Azelastinhydrochlorid sowie die Hilfsstoffe Polysorbat 80, Sorbitol-Lösung, Natriumedetat und Benzalkoniumchlorid unter Rühren auflösen.

Anschließend den Wirkstoff Loteprednoletabonat hochtourig einhomogenisieren, bis eine gleichmäßige Suspension entstanden ist. Danach auf das Endvolumen von 50 Liter mit gereinigtem Wasser auffüllen und weiter homogenisieren. Anschließend die Suspension evakuieren um die entstandenen Luftblasen zu entfernen. Die entstandene Suspension wird anschließend in Flaschen abgefüllt, welche danach mit einer geeigneten Nasenspraypumpe versehen werden.

Patentansprüche

1. Gemisch, umfassend ein Soft-Steroid und mindestens ein Antihistaminikum in fixer oder freier Kombination.
2. Gemisch nach Anspruch 2, dadurch gekennzeichnet, daß es sich bei dem Antihistaminikum um ein topisch verabreichbares Antihistaminikum handelt.
3. Gemisch nach den Ansprüchen 1 oder 2, dadurch gekennzeichnet, daß es sich bei dem Antihistaminikum um Azelastin und/oder Levocabastin handelt.
4. Gemisch nach einem der voranstehenden Ansprüche, dadurch gekennzeichnet, daß es sich bei dem Soft-Steroid um Loteprednol oder einen pharmazeutisch verträglichen Ester davon handelt.
5. Gemisch nach einem der voranstehenden Ansprüche, dadurch gekennzeichnet, daß es sich bei dem Soft-Steroid um Loteprednol Etabonat handelt.
6. Arzneimittel zur Behandlung von Erkrankungen der unteren und/oder oberen Atemwege und/oder zur Behandlung von Allergien, enthaltend als Wirkstoffe ein Soft-Steroid und mindestens ein topisch verabreichbares Antihistaminikum in fixer oder freier Kombination, gegebenenfalls zusammen mit üblichen Hilfs- oder Trägerstoffen.
7. Arzneimittel nach Anspruch 6, dadurch gekennzeichnet, daß es gleichzeitig, nacheinander oder unabhängig voneinander intranasal oder intraocular verabreicht werden kann.
8. Arzneimittel nach den Ansprüchen 6 oder 7, dadurch gekennzeichnet, daß es sich dabei um eine inhalierbare flüssige oder feste Zubereitung handelt.
9. Arzneimittel nach Anspruch 6, dadurch gekennzeichnet, daß das Antihistaminikum auch oral verabreicht werden kann.
10. Verfahren zur Herstellung eines Arzneimittel zur Behandlung und Prophylaxe von Atemwegserkrankungen und/oder Allergien, enthaltend als Wirkstoffe ein Soft-Steroid und mindestens ein Antihistaminikum, dadurch gekennzeichnet, daß man das Soft-Steroid und den oder die Antihistaminika einzeln oder zusammen, gegebenenfalls zusammen mit üblichen Hilfs- oder Trägerstoffen, vermischt und die so erhaltene Mischung in geeignete Darreichungsformen überführt.
11. Verwendung der fixen oder freien Kombination von einem Soft-Steroid und einem Antihistaminikum zur Herstellung eines Arzneimittels zur Behandlung und Prophylaxe von Atemwegserkrankungen und/oder Allergien.
12. Verwendung der fixen oder freien Kombination von einem Soft-Steroid und einem Antihistaminikum zur Herstellung eines Arzneimittels zur Behandlung von allergischer Rhinitis und Rhinokonjunktivitis.
13. Verwendung der fixen oder freien Kombination von einem Soft-Steroid und einem Antihistaminikum zur Herstellung eines Arzneimittels zur Behandlung von Rhinorrhoe.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61K 31/435, 31/55, 31/445, 31/57 // (A61K 31/57, 31:435, 31:445, 31:55)

A1

(11) International Publication Number: **WO 97/01337**

(43) International Publication Date: 16 January 1997 (16.01.97)

(21) International Application Number: PCT/US96/10789

(22) International Filing Date: 25 June 1996 (25.06.96)

(30) Priority Data:
08/496,814 29 June 1995 (29.06.95) US

(71) Applicant: McNEIL-PPC, INC. [US/US]; 7050 Camp Hill Road, Fort Washington, PA 19034 (US).

(72) Inventor: HELZNER, Eileen; 505 Anthony Drive, Plymouth, PA 19462 (US).

(74) Agents: CIAMPORCERO, Audley, A. et al.; Johnson and Johnson, One Johnson & Johnson Plaza, New Brunswick, NJ 08933-7003 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, 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 the receipt of amendments.

(54) Title: THE COMBINATION OF TOPICAL NASAL ANTIHISTAMINES AND TOPICAL NASAL STEROIDS

(57) Abstract

Nasal spray or nasal drops for the treatment of allergic rhinitis are disclosed comprising: a) an effective amount of a topical antihistamine to relieve histamine mediated symptoms where said topical nasal antihistamine is selected from the group consisting of levocabastine, azelastine and azatadine; b) an effective amount of a topical nasal steroid to reduce inflammation where said nasal steroid is selected from the group consisting of beclomethasone, flunisolide, triamcinolone, dexamethasone and budesonide; and c) sterile water.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	**GB**	United Kingdom	**MW**	Malawi
AT	Austria	**GE**	Georgia	**MX**	Mexico
AU	Australia	**GN**	Guinea	**NE**	Niger
BB	Barbados	**GR**	Greece	**NL**	Netherlands
BE	Belgium	**HU**	Hungary	**NO**	Norway
BF	Burkina Faso	**IE**	Ireland	**NZ**	New Zealand
BG	Bulgaria	**IT**	Italy	**PL**	Poland
BJ	Benin	**JP**	Japan	**PT**	Portugal
BR	Brazil	**KE**	Kenya	**RO**	Romania
BY	Belarus	**KG**	Kyrgystan	**RU**	Russian Federation
CA	Canada	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CF	Central African Republic			**SE**	Sweden
CG	Congo	**KR**	Republic of Korea	**SG**	Singapore
CH	Switzerland	**KZ**	Kazakhstan	**SI**	Slovenia
CI	Côte d'Ivoire	**LI**	Liechtenstein	**SK**	Slovakia
CM	Cameroon	**LK**	Sri Lanka	**SN**	Senegal
CN	China	**LR**	Liberia	**SZ**	Swaziland
CS	Czechoslovakia	**LT**	Lithuania	**TD**	Chad
CZ	Czech Republic	**LU**	Luxembourg	**TG**	Togo
DE	Germany	**LV**	Latvia	**TJ**	Tajikistan
DK	Denmark	**MC**	Monaco	**TT**	Trinidad and Tobago
EE	Estonia	**MD**	Republic of Moldova	**UA**	Ukraine
ES	Spain	**MG**	Madagascar	**UG**	Uganda
FI	Finland	**ML**	Mali	**US**	United States of America
FR	France	**MN**	Mongolia	**UZ**	Uzbekistan
GA	Gabon	**MR**	Mauritania	**VN**	Viet Nam

THE COMBINATION OF TOPICAL NASAL ANTIHISTAMINES AND TOPICAL NASAL STEROIDS

The present invention relates to prevention and treatment of the symptoms of seasonal and perennial allergic rhinitis. More particularly, the present invention relates to the prevention and treatment of the symptoms of seasonal and perennial allergic rhinitis by the application of a combination of topical nasal antihistamines and topical nasal steroids.

BACKGROUND OF THE INVENTION

Seasonal allergic rhinitis is most frequently caused by pollen, pollen fragments and mold spores. The airborne pollens, pollen fragments and mold spores are deposited on the nasal mucosa. In sensitive individuals, rhinitis symptoms develop which include puffy, sore eyes, sneezing, nasal congestion, sinus headaches and fatigue.

The chronic symptoms of perennial allergic rhinitis are most frequently caused by reaction to perennial allergens, such as, house dust mite, mold, cockroach, animal saliva, urine, and dander. The symptoms resemble those of seasonal allergic rhinitis but the duration is year round or episodic depending upon the source of the allergens.

Antihistamines are the primary medicaments employed to treat allergic rhinitis. Antihistamines are helpful to control sneezing, itching, and rhinorrhea as well as associated ocular symptoms but are ineffective in relieving nasal blockage. Antihistamines compete with histamine for binding to H_1 receptors and thereby prevent the action of histamine which includes bronchospasm, edema, increased mucus secretion and itching.

The antihistamines primarily in use today are orally active and administered. However, intranasally (topically) administered antihistamines, including azelastine and levocabastine have also been shown to be useful antihistamines in the treatment of allergic rhinitis. The intranasally administered antihistamines have a quick onset of action because they are delivered directly to the site of activity.

Also employed to treat allergic rhinitis are nasal steroids, particularly the corticosteroids. Such steroids have powerful effects on immunologic and hormonal processes and are very effective in treating the inflammation which accompanies the allergic reaction. Suitable nasal steroids known in use today include beclamethasone, flunisolide, triamcinolone, dexamethasone and budesonide.

SUMMARY OF THE INVENTION

There is provided by the present invention a nasal spray or nasal drops for the treatment of allergic rhinitis comprising:

a) an effective amount of a topical antihistamine to relieve histamine mediated symptoms where said topical nasal antihistamine is selected from the group consisting of levocabastine, azelastine and azatadine;

b) an effective amount of a topical nasal steroid to reduce inflammation where said nasal steroid is selected from the group consisting of beclomethasone, flunisolide, triamcinolone, dexamethasone and budesonide; and

c) sterile water.

DETAILED DESCRIPTION OF THE INVENTION

The topical antihistamines herein are potent H^1 receptor antagonists which relieve the histamine mediated symptoms, i.e. sneezing, runny nose, itchy nose, etc. The H^1 receptor antagonists block the receptor sites and thereby block the expression of the histamine effect. Thus, persons skilled in the art understand that only a sufficient amount of the antihistamine should be administered to relieve histamine mediated symptoms and no more. This amount will vary depending on whether levocabastine, azelastine or azatadine is employed. In the case of levocabastine from about 0.05 to about 10 mg and preferably from about 0.5 to about 5 mg should be administered in this combination every 4 to 12 hours. In the case of azelastine from about 0.05 to about 10 mg and preferably from about 0.5 to about 5 mg should be administered in this combination every 4 to 12 hours. In the case of azatadine, from about 0.05 to about 10 and preferably from about 0.5 to about

5 mg should be administered in this combination every 4 to 12 hours. To achieve these dosage ranges, levocabastine should constitute of the nasal spray or nasal drops composition from about 0.2 to about 40 mg/ml and preferably from about 2 to about 20 mg/ml. To achieve these dosage ranges, azelastine should constitute of the nasal spray or nasal drops composition from about 0.2 to about 40 mg/ml and preferably from about 2 to about 20 mg/ml. Similarly, azatadine should constitute from about 0.2 to about 40 mg/ml and preferably from about 2 to about 20 mg/ml.

Levocabastine as used herein includes levocabastine and its pharmaceutically acceptable acid addition salts. Suitable salts include the hydrochloric, hydrobromic, sulfuric, nitric, acetic, propionic, butanedioic, etc. salts. The preferred salt is hydrochloric. Levocabastine, (-)-[3S-1(cis),3,4]-1-[4-cyano-4-(4-fluorophenyl)cyclohexyl]-3-methyl-4-phenyl-4-piperidine carboxylic acid, is a well known compound and may be prepared by the method of U.S. Pat. 4,369,184, EP 34,415 or Stokbroekx, R. A., et al., *Drug Dev. Res.* 8: 87-93 (1986).

Azelastine as used herein, includes azelastine and its pharmacutically acceptable salts. Preferred are the acid addition salts, such as, the hydrohalo salts and salts with organic acids. Preferred salts include hydrochloridic hydrobromidic, embonic acid, maleic acid, citric acid and tartaric acid salts. Azelastine, 4-(p-chlorobenzyl)-2-[N-methyl-perhydroazepin-4-yl)-1-(2H)-phthalazinone, is a well known compound and may be prepared according to Belg. Pat. 778,269; Vogelsang et al., U.S. Pat. 3,813,384 and Scheffler et al., Arch. Pharm. 321, 205 (1988).

Azatadine as used herein includes azatadine and its pharmaceutically acceptable salts. Preferred salts of azatadine include its maleate, sulfate, succinate and acetate salts. Aztadine, 4-aza-5-(N-methyl-4-piperidinylidene)-10,11-dinydro-5H-dibenzo[a,d]cycloheptene, is a well known compound and may be prepared according to Belg. Pat. 647,043; U.S. Pat. 3,3577,986 and Villani et al., J. Med. Chem. 15, 750 (1972).

The topical nasal steroids for use herein are corticosteroids which inhibit the release of mediators for the symptoms associated with allergic rhinitis from mast cells and basophils. They also reduce inflammation and

suppress neutrophil chemotaxis. The topical nasal steroids herein have relatively few side effects but are known to cause nasal irritation, drying and epistaxis with use of nasal sprays. Thus, persons skilled in the art understand that only a sufficient amount of nasal steroid should be administered to inhibit mast cell mediator release and inflammation and no more. This amount will vary depending on whether beclomethasone, flunisolide, triamcinolone, dexamethasone or budesonide is employed. Further, the nasal steroids are relatively long acting and alone can be administered once or twice daily. However, when used in conjunction with an active ingredient requiring more frequent administration, the amount of nasal steroid must be adjusted accordingly. For beclomethasone, from about 10 to about 100 mcg, and preferably from about 15 to about 85 mcg should be administered in this combination every 4 to 12 hours. To achieve these dosage ranges, the beclomethasone should constitute of the nasal spray or nasal drops composition from about 0.05 to about 0.5 mg/ml, and preferably from about 0.1 to about 0.3 mg/ml. For flunisolide, from about 30 to about 300 mcg, and preferably from about 50 to about 200 mcg should be administered in this combination every 4 to 12 hours. To achieve these dosage ranges, the flunisolide should constitute of the nasal spray or nasal drops composition from about 0.1 to about 1.0 mg/ml, and preferably from about 0.15 to about 0.5 mg/ml. For triamcinolone, from about 10 to about 100 mcg, and preferably from about 15 to about 85 mcg should be administered in this combination every 4 to 12 hours. To achieve these dosage ranges, the triamcinolone should constitute of the nasal spray or nasal drops composition from about 0.05 to about 0.5 mg/ml, and preferably from about 0.1 to about 0.3 mg/ml. For dexamethasone, from about 40 to about 400 mcg, and preferably from about 60 to about 340 mcg should be administered in this combination every 4 to 12 hours. To achieve these dosage ranges, the dexamethasone should constitute of the nasal spray or nasal drops composition from about 0.2 to about 2.0 mg/ml, and preferably from about 0.4 to about 1.2 mg/ml. For budesonide, from about 40 to about 400 mcg, and preferably from about 60 to about 340 mcg should be administered in this combination every 4 to 12 hours. To achieve these dosage ranges, the budesonide should constitute of the nasal spray or nasal drops composition from about 0.2 to about 2.0 mg/ml, and preferably from about 0.4 to about 1.2 mg/ml.

The corticosteroid topical nasal steroids are, as a general matter, poorly soluble in water. Thus, they are administered in particulate form, as a micronized suspension in a suitable carrier/solvent system. For the treatment of the lung, it is desirable to produce aerosol particle sizes of less than 3 microns. However, in the instant case where it is desirable to treat nasal symptoms, the necessity of producing an aerosol of small particles is removed. For the present invention, it is only necessary to create a stable suspension of the corticosteroid in water which can be delivered by drops or spray directly into the nasal passages. The particle size of the corticosteroid in suspension is not critical so long as the particle is small enough that the amount of compound available for therapeutic activity is not surface area limited and the particle is stable in suspension. The suspension may be maintained with suitable liposomes. Preferably, however, the suspension is maintained by use of solubilizing agents and a suitable surfactant. Solubilizing agents herein include 1,2-propane diol, 1,3-propane diol, polyethylene glycol having a molecular weight of 100 to 800, dipropylene glycol, or ethanol. A suitable surfactant may be a pharmaceutically acceptable non-ionic, anionic or cationic surfactant. Examples of suitable non-ionic surfactants include glycerol fatty acid esters such as glycerol monostearate, glycol fatty acid esters such as propylene glycol monostearate, polyhydric alcohol fatty acid esters such as polyethylene glycol (400) monooleate, polyoxyethylene fatty acid esters such as polyoxyethylene (40) stearate, polyoxyethylene fatty alcohol ethers such as polyoxyethylene (20) stearyl ether, polyoxyethylene sorbitan fatty acid esters such as polyoxyethylene sorbitan monostearate or polysorbate 20, fatty acid ethanolamides and their derivatives such as the diethanolamide of stearic acid, and the like. Examples of suitable anionic surfactants are soaps including alkali soaps, such as sodium, potassium and ammonium salts of aliphatic carboxylic acids, usually a fatty acids, such as sodium stearate. Organic amine soaps, also included, include organic amine salts of aliphatic carboxylic acids, usually fatty acids, such as triethanolamine stearate. Another class of suitable soaps is the metallic soaps, salts of polyvalent metals and aliphatic carboxylic acids, usually fatty acids, such as aluminum stearate. Examples of suitable cationic surfactants include amine salts such as octadecyl ammonium chloride, quarternary ammonium compounds such as benzalkonium chloride. Other examples of these and other suitable surfactants can be found in "Pharmaceutical Emulsions and Emulsifying Agents" by Lawrence M. Spatton, second edition; The Chemist and Druggist,

London; "Emulsions' Theory and Practice" by Paul Becher, Reinhold Publishing Corporation, New York; and "Detergents and Emulsifyers, 1969 Annual" by John M. McCutcheon, Morristown, N.J., the disclosures thereof being incorporated herein by reference.

Only sufficient solubilizing agent and surfactant should be employed to stabilize the suspension/emulsion. Generally there should be employed from about 5 to about 30% w/v and preferably from 10 to about 25% w/v of cosolvent. Likewise, there should be employed from about 0.1 to about 10% w/v and preferably from about 0.5 to about 5% w/v of surfactant.

Beclamethasone as used herein includes beclamethasone, beclamethasone acetate, beclamethasone valerate, beclamethasone propionate, beclamethasone dipropionate and the like, including the hydrates thereof. Beclamethose, 9-chloro-11,17,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione, may be obtained commercially and is prepared according to Brit. Pat. 912,378 and Brit. Pat. 901,093. Beclamethasone is commercially available.

Flunisolide as used herein includes flunisolide and flunisolide acetate and hydrates thereof. Flunisolide, 6-fluoro-11,21-dihydroxy-16,17-[(1-methylethylidene)bis(oxy)]pregna-1,4-diene-3,20-dione, may be prepared using *S. roseochromogenes* as in Brit. Pat. 933,867 and Chem. Abst. 60, 3070f (1964) or using *Cunninghamella blakesleeana* as in U.S. pat. 3,124,571. Flunisolide is also prepared in 4,273,710. Flunisolide is commercially available.

Triamcinolone as used herein includes triamcinolone and its 16-α, 21-diacetate; triamcinolone acetonide, and its 21-acetate, 21-disodium phosphate, and 21-hemisuccinate; triamcinolone benetonide and triamcinolone hexacetonide, including hydrates thereof. Triamcinolene, 9-fluoro-11,16,17,21-tetrahydroxypregna-1,4-diene-3,20-dione, may be prepared according to Bernstein et al., *J. Am. Chem. Soc.* 78, 5693 (1956) and 81, 1689 (1959); Thoma et al., *J. Am. Chem. Soc.* 79, 4818 (1957); U.S. Pat. 2,789,118 or U.S. Pat. 3,021,347. Triamcinolone acetonide may be prepared by stirring a suspension of triamcinolone in acetone in the presence of a trace of perchloric acid. Triamcinolone benetonide may be prepared according to Ger. Pat. 2,047,218 or U.S. Pat. 3,749,712. Triamcinolone

hexacetonide may be prepared according to U.S. pat. 3,457,348. The triamcinolone and derivatives as taught herein have been sold or are available commercially.

Dexamethasone as used herein includes dexamethasone and its 21-phosphate, 21-acetate, 21-phosphate disodium salt, 21-dimethylaminoacetate, 21-isonicotinate, 17,21-dipropionate and 21-palmitate. Dexamethasone, (11ß, 16α)-9-fluoro-11,17,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione, may be prepared according to Arth et al., *J. Am. Chem. Soc.* 80, 3161 (1958); Oliveto et al., J. Am. Chem. Soc. 80, 4431 (1958); U.S. Pat. 3,007,923; Ger. Pat. 1,113,690 or Brit. Pat. 869,511. Dexamethasone is commercially available.

Budesonide as used herein includes budesonide and its pharmaceutically acceptable salts. Preferred salts of budesonide include its palmitate, laurate, myristate, stearate, oleate, valerate and acetate salts. Budesonide, 16,17-butylidenebis(oxy)-11,21-dihydroxypregna-1,4-diene-3,20-dione, is a well known compound and may be prepared according to U.S. Pat. No. 3,929,768, GB Pat. No. 1,429,922, or A. Thalen, R. L. Brattsand, Arzneimittel Forsch. 29, 1787 (1979).

The nasal spray or nasal drop formulation herein can contain, in addition to the compounds discussed above antimicrobial agents, antioxidants, agents to increase viscosity, isotonic agents, buffers, solubilizing agents, surface active agents and the like. Suitable antimicrobial agents include chlorobutanol, phenylmercuric nitrate, phenyl ethyl alcohol, thimerosal, the quaternary ammonium germicides, such as, benzalkonium chloride, benzethonium chloride or cetylpyridium chloride. Suitable antioxidants include sodium sulfite, sodium ascorbate, oxime sulfate, etc. The preferred isotonic agent is sodium chloride however, other isotonic agents such as dextrose, boric acid and sodium tartrate may be employed. The object of the buffer is to adjust the pH to one compatible with nasal mucous membranes and to stabilize the active ingredient. Ideally the target pH should vary between about 4 and about 6.5. Suitable buffers included phthalate buffers, borate buffers, phosphate buffers, such as $HPO_4^{2-}/H_2PO_4^-$, acetate buffers, such as acetic acid/sodium acetate, a bicarbonate buffer such as CO_2/HCO_3, or a citrate buffer, such as citric acid/citrate, also it may be

adjusted by simply adding an acid such as HCl to achieve the desired acidity. Suitable agents to increase viscosity include polyvinyl alcohol, cellulose derivatives, polyvinylpyrollidone, polysorbates or glycerine. Suitable surface active agents improve absorption by the nasal mucosa and include polyoxyl 40 stearate, polyoxyethylene 50 stearate, polysorbate 80 and octoxynol.

In general, the concentration of the additives will be in the range as follows:

Additive	% W/V
antimicrobial agent	0.001 - 2.0
antioxidant	0.01 - 0.20
isotonic agent	0.01 - 0.50
solubilizing agents	0.01 - 1.0
viscosity builders	0.1 - 2.0
surface active agents	0.01 - 1.0

The buffer should be added in sufficient amount to achieve the pH range stated above of about 4.0 to about 6.5.

Aerosol formulations and nose drops are prepared as per known techniques. The water employed should be of an appropriate pharmaceutical grade of purified water. These formulations should be administered by drop or spray every 4 to 6 hours to obtain the desired relief.

WHAT IS CLAIMED IS:

1. A nasal spray or nasal drops formulation comprising:

a) an effective amount of a topical antihistamine to relieve histamine mediated symptoms where said topical nasal antihistamine is selected from the group consisting of levocabastine, azelastine and azatadine;

b) an effective amount of a topical nasal steroid to reduce inflammation where said nasal steroid is selected from the group consisting of beclomethasone, flunisolide, triamcinolone, dexamethasone and budesonide; and

c) sterile water.

2. The formulation of claim 1 wherein said topical nasal antihistamine is levocabastine and said topical nasal steroid is selected from the group consisting of beclomethasone, flunisolide, triamcinolone, dexamethasone and budesonide.

3. The formulation of claim 1 wherein said topical nasal antihistamine is azelastine and said topical nasal steroid is selected from the group consisting of beclomethasone, flunisolide, triamcinolone, dexamethasone and budesonide.

4. The formulation of claim 1 wherein said topical nasal antihistamine is azatadine and said topical nasal steroid is selected from the group consisting of beclomethasone, flunisolide, triamcinolone, dexamethasone and budesonide.

5. The formulation of claim 1 wherein said levocabastine constitutes of the nasal spray or nasal drops composition from about 0.2 to about 40 mg/ml; said azelastine constitutes of the nasal spray or nasal drops composition from about 0.2 to about 40 mg/ml; and said azatadine constitutes of the nasal spray or nasal drops composition from about 0.2 to about 40 mg/ml.

6. The formulation of claim 1 wherein said beclomethasone constitutes of the nasal spray or nasal drops composition from about 0.05 to about 0.5

mg/ml; said flunisolide constitutes of the nasal spray or nasal drops composition from about 0.1 to about 1.0 mg/ml; said triamcinolone constitutes of the nasal spray or nasal drops composition from about 0.05 to about 0.5 mg/ml; said dexamethasone constitutes of the nasal spray or nasal drops composition from about 0.2 to about 2.0 mg/ml; and said budesonide constitutes of the nasal spray or nasal drops composition from about 0.2 to about 2.0 mg/ml.

INTERNATIONAL SEARCH REPORT

Inter .onal Application No
PCT/US 96/10789

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/435 A61K31/55 A61K31/445 A61K31/57 //(A61K31/57, 31:435,31:445,31:55)

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.
X	DRUGS, vol. 45, no. 4, 1993, pages 518-527, XP000603981 HORAK F.: "SEASONAL ALLERGIC RHINITIS" see abstract see page 521, left-hand column, line 8 - page 522, left-hand column, line 41 see page 526, right-hand column, line 1 - line 15 --- -/--	1-6

[X] Further documents are listed in the continuation of box C. [ ] 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
29 October 1996	14. 11. 96

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	Economou, D

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

INTERNATIONAL SEARCH REPORT

Inter onal Application No
PCT/US 96/10789

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CLINICAL PHARMACY, vol. 8, no. 7, July 1989, pages 474-485, XP000603999 DELAFUENTE J.C., ET AL.: "PHARMACOTHERAPY OF ALLERGIC RHINITIS" see abstract see page 477; table 1 see page 479, left-hand column, line 13 - page 481, left-hand column, line 35 see page 482, left-hand column, paragraph 3 see page 483, left-hand column, paragraph 2 - paragraph 3 ---	1-6
Y	J.ALLERGY CLIN. IMMUNOL., vol. 82, no. 5, November 1988, pages 890-900, XP000603998 BUSSE W.: "NEW DIRECTIONS AND DIMENSIONS IN THE TREATMENT OF ALLERGIC RHINITIS" see page 890, left-hand column, paragraph 1 see page 892; table II see page 891, right-hand column, paragraph 4 - page 897, right-hand column, paragraph 2 see page 898, right-hand column, paragraph 1 see page 899, left-hand column, paragraph 2 ---	1-6
Y	CLINICAL IMMUNOTHERAPEUTICS, vol. 4, no. 4, April 1995, pages 270-278, XP000604030 LUND V.: "PRACTICAL APPLICATION OF THE INTERNATIONAL CONSENSUS ON THE MANAGEMENT OF RHINITIS" see abstract see page 273, left-hand column, paragraph 2 - page 274, right-hand column, paragraph 3 see page 277; table V ---	1-6
P,Y	INTERNISTA, vol. 3, September 1995, pages 167-170, XP000604083 PURELLO D'AMBROSIO F., ET AL.: "LEVOCABASTINA VERSUS FLUNISOLIDE NEL TRATTAMENTO DELLA RINITE ALLERGICA PERENNE" see abstract see page 168, left-hand column, line 5 - line 39 see page 168, right-hand column, last paragraph - page 169, left-hand column, line 6 --- -/--	1-6

1

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

INTERNATIONAL SEARCH REPORT

Inter. nal Application No
PCT/US 96/10789

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	HOSPITAL PRACTICE, vol. 31, no. 6, 15 June 1996, pages 61-73, XP000604174 HOLLINGSWORTH: "ALLERGIC RHINOCONJUCTIVITIS: CURRENT THERAPY" see page 67, middle column, paragraph 2 - page 71, middle column, paragraph 3 see page 67; table 4 ---	1-6
P,Y	ACTA OTORHINOLARYNGOL. , vol. 50, no. 1, January 1996, pages 25-32, XP000604028 WANG D., ET AL.: "THE ACTIVITY OF RECENT ANTI-ALLERGIC DRUGS IN THE TREATMENT OF SEASONAL ALLERGIC RHINITIS" see abstract see page 25, right-hand column, line 1 - line 4 see page 26, right-hand column, line 3 - line 13 see page 28, left-hand column, paragraph 2 - paragraph 4 see page 28, right-hand column, paragraph 3 - page 29, left-hand column, paragraph 2 see page 29, right-hand column, paragraph 1 - paragraph 2 see page 30, right-hand column, paragraph 2 - page 31, right-hand column, paragraph 1	1-6
Y	& MEETING OF THE ROYAL BELGIAN SOCIETY FOR ENT, HEAD AND NECK SURGERY, February 1995, BRUSSELS, -----	1-6

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

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 780 127 A1

(12) EUROPEAN PATENT APPLICATION

(43) Date of publication:
25.06.1997 Bulletin 1997/26

(21) Application number: **96308852.1**

(22) Date of filing: **05.12.1996**

(51) Int Cl.[6]: **A61K 31/57**, A61K 31/58, A61K 31/56, A61K 31/495, A61K 31/445, A61K 31/55 // (A61K31/56, 31:495), (A61K31/56, 31:445), (A61K31/56, 31:55), (A61K31/57, 31:495), (A61K31/57, 31:445), (A61K31/57, 31:55), (A61K31/58, 31:495), (A61K31/58, 31:445)

(84) Designated Contracting States:
AT BE CH DE DK ES FI FR GB GR IE IT LI LU NL PT SE

(30) Priority: **19.12.1995 US 574791**

(71) Applicant: **THE PROCTER & GAMBLE COMPANY**
Cincinnati, Ohio 45202 (US)

(72) Inventor: **Cramer, Ronald Dean**
Cincinnati, Ohio 45215 (US)

(74) Representative: **Woof, Victoria**
Procter & Gamble Pharmaceuticals Ltd.,
Patent Department,
Lovett House,
Lovett Road
Staines, Middlesex TW18 3AZ (GB)

(54) A nasal spray containing a steroid and a antihistamine

(57) The present invention relates to novel nasal spray compositions comprising a safe and effective amount of a glucocorticosteroid and an antihistamine possessing leukotriene inhibiting properties.

EP 0 780 127 A1

Printed by Jouve, 75001 PARIS (FR)

Description

TECHNICAL FIELD

The present invention relates to novel nasal spray compositions comprising a safe and effective amount of a glucocorticosteroid and an antihistamine.

BACKGROUND OF THE INVENTION

Allergic disorders remain a leading cause of both acute and chronic illnesses the world over. These illnesses are often times present in the form of acute or chronic rhinoconjunctivitis. The symptoms of allergic rhinoconjunctivitis are reddening of the eyes, ocular secretions, nasal congestion, ocular and palatial irritation, sneezing and hypersecretion. These symptoms occur following exposure to allergens. The most common allergens are grass and/or tree pollens, hence, allergic rhinoconjunctivitis is most common during the spring and summer months.

The symptoms of allergic rhinoconjunctivitis are believed to be due primarily to the stimulation of H-1 receptors by histamine, followed by reflexive activation of parasympathetic nerves causing increases in nasal secretion and obstruction. Histamine is initially released from the tissue mast cells upon sensitization of the mast cells. This sensitization results when airborne allergens combine with specific IgE antibodies attached to mast cell membranes.

Antihistamines and/or decongestants have traditionally been the drugs of choice in treating allergic rhinoconjunctivitis. Other forms of therapy include the use of cromolyn sodium, hypertonic salt solutions or immunotherapy.

In addition, Hagen et al., U.S. Patent 4,767,612, discloses nasal corticosteroid therapy as an effective means of treating allergic rhinoconjunctivitis; and is herein incorporated by reference in its entirety. Notwithstanding the many disclosures in the area of allergic rhinoconjunctivitis, there is still a need for additional formulations which provide improved symptomatic relief with increased user acceptance and compliance.

The present inventor has found that by combining a nasal corticosteroid with a leukotriene inhibiting antihistamine, improved intranasal compositions result, providing improved relief of symptoms generally associated with either seasonal or perennial allergic rhinoconjunctivitis.

It is, therefore, an object of the present invention to provide pharmaceutical compositions having improved effectiveness in the treatment of symptoms generally associated with either seasonal or perennial allergic rhinoconjunctivitis.

A further object of the present invention is to provide a safe and effective method for treating the symptoms of seasonal or perennial allergic rhinoconjunctivitis.

These objects and other objects will become more apparent from the detailed description that follows.

SUMMARY OF THE INVENTION

The present invention relates to pharmaceutical compositions for nasal administration comprising:

a) a safe and effective amount of a glucocorticoid selected from the group consisting of beclomethasone, flunisolide, triamcinolone, fluticasone, mometasone, budesonide, pharmaceutically acceptable salts thereof and mixtures thereof;

b) a safe and effective amount of a leukotriene inhibiting antihistamine selected from the group consisting of cetirizine, loratadine, azelastine, pharmaceutically acceptable salts thereof, optically active racemates thereof and mixtures thereof; and

c.) an intranasal carrier.

The intranasal carrier of the present invention is preferably aqueous.

The present invention also relates to a method for the treatment of symptoms associated with seasonal or perennial allergic rhinoconjunctivitis comprising the administration of a safe and effective amount of the intranasal pharmaceutical compositions of the present invention. By "symptoms of seasonal or perennial allergic rhinoconjunctivitis" or "symptoms associated with seasonal or perennial allergic rhinoconjunctivitis," is meant ocular and palatial irritation, ocular secretions, reddening of the eyes, sneezing, mucoid hypersecretion, nasal congestion and itching.

By "safe and effective amount," as used herein, is an amount that is effective to mitigate and/or treat the symptoms for which the active ingredient is indicated in a human without undue adverse side effects commensurate with a reasonable risk/benefit ratio.

By "leukotriene inhibiting antihistamine,"as used herein, is meant an antihistamine effective in inhibiting or reducing *in vivo* the biosynthesis of and/or cellular release of leukotrienes or otherwise modulating mammalian leukotriene levels.

The pH of the compositions is preferably from about 4.5 to about 9, more preferably from about 6 to about 7.

All percentages and ratios herein are by weight unless otherwise specified. Additionally, all measurements are

made at 25°C unless otherwise specified.

DETAILED DESCRIPTION OF THE INVENTION

The compositions of the present invention contain the essential components as well as various optional components as indicated below.

More specifically, the compositions of the instant invention are for nasal administration and contain a therapeutically effective amount of the herein described pharmaceutical agents. They are preferably provided as isotonic aqueous solutions, suspensions or viscous compositions which may be buffered to a selected pH.

Essential Ingredients

Glucocorticoid Agents

Agents within this class have potent glucocorticoid activity and weak mineralocorticoid activity. Glucocorticoid agents most useful to the present invention include those selected from the group consisting of beclomethasone, flunisolide, triamcinolone, fluticasone, mometasone, budesonide, pharmaceutically acceptable salts thereof and mixtures thereof.

When used in the compositions of the present invention, the glucocorticoid component is preferably present at a concentration of from about 0.001% to about 0.2%, more preferably from about 0.01% to about 0.1%.

Leukotriene Inhibiting, Antihistaminic Agents

Antihistamines useful to the present invention are histamine H-1 receptor antagonists which also reduce mammalian leukotriene levels. Such H-1 receptor antihistamines may be selected from among the following groups of antihistamines: piperazines, phenothiazines, piperidines.

Examples of useful leukotriene inhibiting antihistamines include cetirizine, loratadine, azelastine and the like, optically active racemates thereof, pharmaceutically acceptable salts thereof and mixtures thereof. When used in the compositions of the present invention, the antihistamine component is preferably present at a concentration of from about 0.01% to about 4.0%, more preferably from about 0.01% to about 1%.

Pharmaceutically-Acceptable Aqueous Nasal Carrier.

One other essential component of the present invention is a pharmaceutically-acceptable intranasal carrier. Preferred for use herein are aqueous saline solution carriers. These solutions which generally contain sodium chloride as the salt are fully described in Remington's Pharmaceutical Sciences, 17th edition (1985) p. 835, which is herein incorporated by reference. The salt is present in the solution at a level of about 0.01% to about 2%, preferably from about 0.5% to about 1.0%.

The combination of any of the above described antihistamines and glucocorticoids can be conveniently administered nasally to warm-blooded animals to elicit the desired therapeutic response by formulating it into a nasal dosage form, together with a nontoxic pharmaceutically-acceptable nasal carrier. Suitable nontoxic pharmaceutically-acceptable nasal carriers are known to those skilled in the art and are also fully disclosed in Remington's Pharmaceutical Sciences, 17th edition, 1985. Obviously, the choice of suitable carrier forms will depend on the exact nature of the particular nasal dosage form required, e.g., whether the drug(s) is to be formulated into a nasal solution (for use as drops or as a spray), a nasal suspension, a nasal ointment, a nasal gel or another nasal form. Preferred nasal dosage forms are solutions, suspensions and gels, which normally contain sodium chloride in a major amount of water (preferably purified water) in addition to the antihistamine and glucocorticoid. Minor amounts of other ingredients such as pH adjusters (e.g., an acid such as HCl), emulsifiers or dispersing agents, buffering agents, preservatives, wetting agents and jelling agents (e.g., methylcellulose) may also be present. Most preferably, the nasal composition is isotonic, i.e., it has the same osmotic pressure as blood and lacrimal fluid.

Preferably the composition is applied to the nasal mucosa via topical application of a safe and effective amount of the composition to treat nasal symptoms. The amount of the antihistamine and glucocorticoid combination and frequency of topical application to the nasal mucosa may vary, depending upon personal or medical needs, but it is suggested, as an example, that topical application range from about once per day to about four times daily, preferably twice daily, most preferably once daily. As a practical matter the selected therapeutic compositions will normally be prepared in unit dosage forms or actuations to contain therapeutically effective amounts of the selected antihistamine and glucocorticoid combination. In specific instances fractions of these dosage units or multiple dosage units will be employed. Typically, dosage units may be prepared to deliver from about 0.5 mcg to about 100 mcg of the glucocorticoid

agent and from about 5 mcg to about 1000 mcg of the antihistaminic agent per spray actuation (e.g., 50 mg to about 200 mg of the spray composition). A typical dose contains one to four sprays per nostril.

Optional Ingredients

Optional ingredients useful in the present invention include decongestants. Decongestants useful to the present invention may be selected from among the class of sympathomimetic agents; examples of which include pseudoephedrine, desoxyephedrine, propylhexedrine, phenylpropanolamine, xylometazoline, phenylephrine, tetrahydrozoline, naphazoline, oxymetazoline, tramazoline and pharmaceutically acceptable salts thereof. Also useful as decongestants are the 5-(2-imidazolinylamino)benzimedazole compounds. Mixtures of these decongestants can also be used.

When used in the compositions of the present invention, the sympathomimetic agents may be incorporated at concentrations, preferably, of from about 0.01% to about 0.5%, more preferably from about 0.05% to about 0.1%.

The compositions of the present invention may also contain antiallergics. Suitable antiallergics include, but are not limited to, cromolyn, ketotifen, N-allyl-(dichloro-3, 4-benzyl)-2-methylamino-2-propanol-1, AP-582 (Pharmaprojects No. 3055-under investigation by Ariad Pharmaceuticals), Andolast, oxatamide and pharmaceutically-acceptable salts thereof. Mixtures of these antiallergics may also be used.

Similarly, mucolytics such as acetylcysteine and anticholinergics such as ipratropium bromide may also be used in the compositions of the present invention.

Also of optional use in the compositions of the present invention are nonopiate analgesics such as oxaprozin. The intranasal use of oxaprozin is described in Namiki et al., Studies on improvement of pharmaceutical preparations prescribed in hospitals. VI. oxaprozin nasal spray, Drug Design and Delivery 1988;2:pp. 311-321, herein incorporated by reference. Further examples of preferred nonopiate analgesics include, but are not limited to, acetaminophen, acetylsalicylic acid, ibuprofen, etodolac, fenbuprofen, fenoprofen, flurbiprofen, indomethacin, ketoprofen, naproxen, pharmaceutically-acceptable salts thereof, optically active racemates thereof and mixtures thereof. Still further examples of such drugs are disclosed in U.S. Patent No. 4,522,828, to Sunshine et al., issued June 11, 1985; this patent being incorporated herein by reference in its entirety.

Synthetic opiate analgesics such as butorphanol may also be incorporated into the compositions of the present invention. The intranasal use of butorphanol is described in Baumel, Migraine: A pharmacologic review with newer options and delivery modalities, Neurology 1994;44(supp):pp. s13-s17, herein incorporated by reference. Further examples of preferred synthetic opioid analgesics include alfentanil, buprenorphine, fentanyl, meperidine, methadone, nalbuphine, natrexone, propoxyphene, pentazocine, sufenanil, pharmaceutically-acceptable salts thereof and mixtures thereof.

Compounds commonly known as lipoxygenase inhibitors and receptor antagonists are also optionally useful in the compositions of the present invention. Suitable lipoxygenase inhibitors are described in U.S. Patent 4,873,259, to Summers et al., issued October 10 1989 and European Patent Application 318093, both of which are herein incorporated by reference. Lipoxygenase antagonists suitable for use in the present invention include Zafirlukast (Accolate, Zeneca).

Leukotriene receptor antagonists may also be incorporated into the compositions of the present invention. Suitable examples include, but are not limited to, experimental agents such as LY171883, Wy-45,911, LY163443, ONO-RS-411 and ONO-RS-347 and ICI 198,615. A more detailed discussion of leukotriene receptor antagonists is found in Fleisch, J. H., Development of Cysteinyl Leukotriene Receptor Antagonists, Vol. 12 Advances in Inflammation Research 173-189 (A. Lewis et al. ed. 1988), herein incorporated by reference in its entirety.

Various aromatic components (e.g., aldehydes and esters) may also be used. These aromatics include, for example, menthol, camphor, eucalyptol, benzaldehyde (cherry, almond); citral (lemon, lime); neral; decanal (orange, lemon); aldehyde C-8, aldehyde C-9 and aldehyde C-12 (citrus fruits); tolyl aldehyde (cherry, almond); 2,6-dimethyl-octanal (green fruit); and 2-dodecenal (citrus, mandarin). Additional aromatic components suitable for use in the present invention include those described in U.S. Patent 4,136,163 to Watson et al., U.S. Patent 4,459,425 to Amano et al., and U.S. Patent 4,230,688 to Rowsell et al.; all of which are herein incorporated by reference. Mixtures of these aromatics can also be used.

The desired isotonicity of the compositions of this invention may be accomplished using, for example, the sodium chloride already present, or other pharmaceutically-acceptable agents such as dextrose, boric acid, citric acid, sodium tartrate, sodium phosphate, potassium phosphate, propylene glycol or other inorganic or organic solutes or mixtures thereof. Sodium chloride is preferred particularly for buffers containing sodium ions. Further examples of sodium chloride equivalents are disclosed in Remington's Pharmaceutical Sciences pp. 1491-1497 (Alfonso Gennaro 18th ed. 1990).

Viscosity of the compositions may be maintained at the selected level using a pharmaceutically-acceptable thickening agent. Methyl cellulose is preferred because it is readily and economically available and is easy to work with. Other suitable thickening agents include, for example, xanthan gum, microcrystalline cellulose, carboxymethyl cellu-

lose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose, carboxyvinyl polymer, carbomer, and the like or pharmaceutical salts thereof. Mixtures of such thickening agents may also be used. The preferred concentration of the thickener will depend upon the agent selected. The important point is to use an amount which will achieve the selected viscosity. Viscous compositions are normally prepared from solutions by the addition of such thickening agents.

Preferred compositions within the scope of this invention will contain from about 0.01% to about 5% of a humectant to inhibit drying of the mucous membrane and to prevent irritation. Any of a variety of pharmaceutically-acceptable humectants can be employed including, for example sorbitol, propylene glycol, polyethylene glycol, glycerol or mixtures thereof. As with the thickeners, the concentration will vary with the selected agent, although the presence or absence of these agents, or their concentration is not an essential feature of the invention.

Enhanced absorption across the nasal membrane can be accomplished employing a therapeutically acceptable surfactant. Typical useful surfactants for these therapeutic compositions include polyoxyethylene derivatives of fatty acid partial esters of sorbitol anhydrides such as Polysorbate 80, Polyoxyl 40 Stearate, Polyoxylethylene 50 Stearate and Octoxynol, as well as Oxyethylated tertiary octyl phenol formaldehyde polymer (available from Sterling Organics as tyloxapol) or mixtures thereof. The usual concentration is from 0.5% to 10% based on the total weight.

A pharmaceutically-acceptable preservative is generally employed to increase the shelf life of the compositions of the present invention. Benzyl alcohol is suitable, although a variety of preservatives including, for example, parabens, phenylethyl alcohol, thimerosal, chlorobutanol, phenylmecuric acetate or benzalkonium chloride may also be employed. The most preferred preservative system for use herein comprises a combination of benzalkonium chloride, chlorhexidine gluconate and disodium EDTA. A suitable concentration of the preservative will be from 0.001% to 2% based on the total weight, although there may be appreciable variation depending upon the agent selected Mixtures of these preservatives may also be used.

Other Optional Components. A variety of additional ingredients may be added to the emulsion compositions of the present invention. These additional ingredients include various polymers for aiding the film-forming properties and substantivity of the formulation, antioxidants, and agents suitable for aesthetic purposes such as fragrances, pigments, and colorings.

The compositions can also contain low levels of insoluble ingredients added, for example for visual effect purposes, e.g. thermochromic liquid crystalline materials such as the microencapsulated cholesteryl esters and chiral nematic (nonsterol) based chemicals such as the (2-methylbutyl) phenyl 4-alkyl(oxy)benzoates available from Hallcrest, Glenview, Illinois 60025, U.S.A. Mixtures of these ingredients may also be used.

EXAMPLES

The following examples further describe and demonstrate embodiments within the scope of the present invention. The examples are given solely for the purpose of illustration and are not to be construed as limitations of the present invention, as many variations thereof are possible without departing from the spirit and scope of the invention.

Example I

The intranasally administered pharmaceutical composition of the present invention is prepared by combining the following components utilizing conventional mixing techniques similar to that described below.

Component	Wgt %
beclomethasone diproprionate, monohydrate	0.042
loratadine	0.200
avicel RC - 591[1]	1.200
dextrose	5.100
polysorbate 80	0.025
benzalkonium chloride	0.040
phenylethyl alcohol	0.250
distilled water	q.s. to vol.

[1] microcrystalline cellulose and sodium carboxymethyl cellulose, supplied by FMC corporation.

In an appropriately sized vessel, the dextrose, polysorbate 80 and benzalkonium chloride are added one at a time to water with mixing, allowing each to dissolve or completely disperse before adding the next. To this is added, with mixing, a premixed slurry of the avicel and water. Upon forming a uniform solution, the beclomethasone, loratadine

and phenylethyl alcohol are added. After all the ingredients are added, purified water is used to bring the batch to the appropriate weight.

Administration of approximately 0.4 grams of the composition is used for topical nasal application to provide relief from allergy or allergy-like symptoms.

Example II

The intranasally administered pharmaceutical composition of the present invention is prepared by combining the following components utilizing conventional mixing techniques similar to that described in Example I.

Component	Wgt %
flunisolide	0.025
cetirizine	0.200
propylene glycol	2.000
polyethylene glycol	1.000
sodium chloride	0.900
ethylenediamine tetraacetic acid	0.050
benzalkonium chloride	0.010
distilled water	q.s. to vol.

Administration of approximately 0.4 grams of the composition is used for topical nasal application to provide relief from allergy or allergy-like symptoms.

Example III

The intranasally administered pharmaceutical composition of the present invention is prepared by combining the following components utilizing conventional mixing techniques similar to that described in Example I.

Component	Wgt %
triamcinolone acetonide	0.050
azelastine HCl	0.070
polysorbate 80	0.050
glycerin	2.000
hydroxypropyl methyl cellulose	1.000
sodium chloride	0.900
ethylenediamine tetraacetic acid	0.050
benzalkonium chloride	0.020
distilled water	q.s. to vol.

Administration of approximately 0.4 grams of the composition is used for topical nasal application to provide relief from allergy or allergy-like symptoms. Additionally, substantially similar results are also obtained using, in whole or in part, equivalent amounts of other glucocorticoid agents such as fluticasone, mometasone, budesonide, pharmaceutically acceptable salts thereof and mixtures thereof. Furthermore, the above described compositions may also contain a decongestant such as pseudoephedrine, phenylpropanolamine, phenylephrine, tetrahydrozoline, naphazoline, oxymetazoline, tramazoline, 5-(2-imidazolinylamino)benzimedazoles, optically active racemates thereof, pharmaceutically acceptable salts thereof and mixtures thereof. Those skilled in the art will quickly realize other suitable ingredients, diluents and dosage forms (or readily ascertain such using routine experimentation) which may further be incorporated into the above compositions without departing from the scope and spirit of the present invention.

Claims

1. A pharmaceutical composition comprising:

    a) a safe and effective amount of a glucocorticoid selected from the group consisting of beclomethasone,

flunisolide, triamcinolone, fluticasone, mometasone, budesonide, pharmaceutically acceptable salts thereof and mixtures thereof;
b) a safe and effective amount of a leukotriene inhibiting antihistamine selected from the group consisting of cetirizine, loratadine, azelastine, pharmaceutically acceptable salts thereof, optically active racemates thereof and mixtures thereof; and
c.) an intranasal carrier.

2. A composition according to Claim 1 in the form of an isotonic aqueous solution

3. A composition according to Claim 1 or 2 wherein the glucocorticoid is selected from the group consisting of beclomethasone, budesonide, fluticasone and mixtures thereof.
4. A pharmaceutical composition according to any of Claims 1-3, which further comprises a sympathomimetic amine selected from the group consisting of pseudoephedrine, desoxyephedrine, propylhexedrine, phenylpropanolamine, xylometazoline, phenylephrine, tetrahydrozoline, naphazoline, oxymetazoline, tramazoline, 5-(2-imidazolinylamino)benzimedazoles, pharmaceutically acceptable salts thereof, optically active racemates thereof and mixtures thereof.
5. A pharmaceutical composition according to any of Claims 1-4, which further comprises a non-steroidal anti inflammatory agent, or optically active racemates thereof and mixtures thereof.
6. A pharmaceutical composition according to any of Claims 1-5, which further comprises a lipoxygenase inhibitor or antagonist, a leukotriene receptor antagonist, a nonopiate analgesic, a mucolytic, an antiallergic, and pharmaceutically acceptable salts thereof and mixtures thereof.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 96 30 8852

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X,Y	ADVANCES IN THERAPY, vol. 12, no. 6, November 1995 - December 1995, USA, pages 340-349, XP000651473 DROUIN ET AL: "ADDING LORATADINE TO TOPICAL NASAL STEROID THERAPY IMPROVES MODERATELY SEVERE SEASONAL ALLERGIC RHINOCONJUNCTIVITIS" * the whole document * ---	1-6	A61K31/57 A61K31/58 A61K31/56 A61K31/495 A61K31/445 A61K31/55 //(A61K31/56, A61K31:495), (A61K31/56, A61K31:445), (A61K31/56, A61K31:55), (A61K31/57, A61K31:495), (A61K31/57, A61K31:445), (A61K31/57, A61K31:55),
X,Y	CLINICAL AND EXPERIMENTAL ALLERGY, vol. 22, no. 10, October 1992, UK, pages 916-922, XP000651660 ARMITAGE ET AL : "INVESTICATION OF THE TENDENCY TO WHEEZE IN POLLEN SENSITIVE PATIENTS" * the whole document * ---	1-6	
X,Y	DRUG INVESTIGATION, vol. 8, no. 4, 1994, UK, pages 225-233, XP000651434 BENINCASA ET AL: "EVALUATION OF FLUTICASONE PROPIONATE AQUEOUS NASAL SPRAY TAKEN ALONE AND IN COMBINATION WITH CETIRIZINE IN THE PROPHYLACTIC TREATMENT OF SEASONAL ALLERGIC RHINITIS" * the whole document * ---	1-6	TECHNICAL FIELDS SEARCHED (Int.Cl.6) A61K
D,Y	US 4 767 612 A (HAGEN NICHOLAS S ET AL) 30 August 1988 * abstract * ---	1,2,4-6	
Y	JAMES E.F. REYNOLDS: "MARTINDALE THE EXTRA PHARMACOPOEIA, 13TH EDITION" 1993 , THE PHARMACEUTICAL PRESS , LONDON XP002028542 PAGE 931: AZELASTINE --- -/--	1-6	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
MUNICH	1 April 1997	Herrera, S

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 96 30 8852

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
Y	EP 0 605 203 A (SENJU PHARMA CO) 6 July 1994 * the whole document * -----	1-6	(A61K31/58, A61K31:495), (A61K31/58, A61K31:445)

TECHNICAL FIELDS SEARCHED (Int.Cl.6)

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
MUNICH	1 April 1997	Herrera, S

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)

THIS PAGE BLANK (USPTO)

UNITED STATES PATENT AND TRADEMARK OFFICE

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

U.S. APPLICATION NUMBER NO.	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
10/518,016	Amar Lulla	TPP31753

INTERNATIONAL APPLICATION NO.	
PCT/GB03/02557	
I.A. FILING DATE	PRIORITY DATE
06/13/2003	06/14/2002

Davis Miller & Mosher
1615 L Street N W
Suite 850
Washington, DC 20036

CONFIRMATION NO. 4912
371 ACCEPTANCE LETTER
OC0000000016667257
OC0000000016667257

Date Mailed: 08/23/2005

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

The applicant is hereby advised that the United States Patent and Trademark Office in its capacity as a Designated / 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:

07/06/2005	07/06/2005
DATE OF RECEIPT OF 35 U.S.C. 371(c)(1), (c)(2) and (c)(4) REQUIREMENTS	DATE OF COMPLETION OF ALL 35 U.S.C. 371 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 (c)(1), (c)(2) and (c)(4) 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:

- Copy of the International Application filed on 12/14/2004
- Copy of the International Search Report filed on 12/14/2004
- Copy of IPE Report filed on 12/14/2004
- Preliminary Amendments filed on 12/14/2004
- Information Disclosure Statements filed on 07/06/2005
- Oath or Declaration filed on 07/06/2005
- U.S. Basic National Fees filed on 12/14/2004
- Assignment filed on 07/06/2005
- Priority Documents filed on 12/14/2004

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)

FRANCINE YOUNG
Telephone: (703) 308-9140 EXT 215

PART 3 - OFFICE COPY

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

UNITED STATES PATENT AND TRADEMARK OFFICE

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

BIBDATASHEET

Bib Data Sheet

CONFIRMATION NO. 4912

SERIAL NUMBER	FILING OR 371(c) DATE / RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
10/518,016	07/06/2005 RULE	514	1614	TPP31753

APPLICANTS

Amar Lulla, Mumbai, INDIA;
Geena Malhotra, Mumbai, INDIA;

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

This application is a 371 of PCT/GB03/02557 06/13/2003

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

UNITED KINGDOM 0213739.6 06/14/2002

Foreign Priority claimed	STATE OR COUNTRY	SHEETS DRAWING	TOTAL CLAIMS	INDEPENDENT CLAIMS
☐ yes ☐ no	INDIA		51	3
35 USC 119 (a-d) conditions met ☐ yes ☐ no ☐ Met after Allowance				
Verified and Acknowledged Examiner's Signature Initials				

ADDRESS

Davis Miller & Mosher
1615 L Street N W
Suite 850
Washington ,DC 20036

TITLE

Combination of azelastine and steroids

FILING FEE RECEIVED	FEES: Authority has been given in Paper No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:
2580	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

COMBINED DECLARATION AND POWER OF ATTORNEY FOR UTILITY PATENT APPLICATION (Includes PCT)	Attorney Docket No. TPP 31753

As a below named inventor, I hereby declare that:

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

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 inventors are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled: COMBINATION OF AZELASTINE AND STEROIDS

the specification of which (check one)

[ ] is attached hereto.

[ ] was filed on _____ as Application Serial No. _____ and was amended on _____. (if applicable)

[X] was filed as PCT International Application No. PCT/GB03/02557 on June 13, 2003, and was filed in the U.S. National Stage on December 14, 2004, as U.S. Patent Application No. 10/518,016.

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 the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I do not know and do not believe the claimed invention was ever known or used in the United States of America before my or our invention thereof, or patented or described in any printed publication in any country before my or our invention thereof or more than one year prior to this application, that the same was not in public use or on sale in the United States of America more than one year prior to this application, that the invention has not been patented or made the subject of an inventor's certificate issued before the date of this application in any country foreign to the United States of America on an application filed by me or my legal representatives or assigns more than twelve months prior to this application.

I hereby claim foreign priority benefits under Title 35, United States Code §119 and/or §365(a)(b) of any foreign application(s) and United States provisional applications 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(s) on which priority is claimed:

Prior Foreign and U.S. Provisional Application(s)			Priority Claimed	
0213739.6	Great Britain	14 June 2002	[X]	[ ]
(Number)	(Country)	Day/Month/Year Filed	Yes	No
_____	_____	_____	[ ]	[ ]
(Number)	(Country)	Day/Month/Year Filed	Yes	No

Attorney Docket No. TPP 31753

I hereby claim the benefit under Title 35, United States Code, §120 and/or §365(c) of any United States application(s) or PCT international application(s) designating the United States of America listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

Application Serial No.	Filing Date	Status (patented, pending, abandoned)

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith; Stevens, Davis, Miller & Mosher, L.L.P.; Anthony P. Venturino, Reg. No. 31,674; James E. Ledbetter, Reg. No. 28,732; Thomas P. Pavelko, Reg. No. 31,689; and Peter N. Lalos, Reg. No. 19,789. Direct all telephone calls to telephone no. 202-785-0100 and faxes to 202-408-5200.

Address all correspondence to 1615 L Street, N.W., Suite 850, Washington, D.C. 20036.

CIPLA Limited retains the power to revoke this Power of Attorney at any time and at its own discretion.

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, First Inventor	Inventor's Signature	Date
Amar LULLA	x	08.06.05
Residence: Mumbai, India INX		Citizenship: Indian
Post Office Address: 131 Maker Towers L, 13th Floor, Cuffe Parade, Colaba, Mumbai 400 005 India		

Full Name of Second, Joint Inventor Geena MALHOTRA	Inventor's Signature ×Gm Malhotra	Date 08·06·05
Residence: Mumbai, India INX		Citizenship Indian
Post Office Address: 4 Anderson House, Opposite Mazgaon Post Office, Mazgaon, Mumbai 400 010 India		
Full Name of Third, Joint Inventor	Inventor's Signature	Date
Residence:		Citizenship
Post Office Address:		

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of

Amar LULLA et al

BOX: Missing Parts

Serial No.: 10/518,016

Filed: December 14, 2004

For: COMBINATION OF AZELASTINE AND STEROIDS

RESPONSE TO NOTIFICATION OF MISSING REQUIREMENTS UNDER 35 USC 371 IN THE UNITED STATES DESIGNATED/ELECTED OFFICE

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

Sir:

Responsive to the Patent Office paper issued May 9, 2005, there is submitted herewith an executed Declaration for the above-identified application. Also submitted herewith is an executed Assignment. A copy of Form PCT/DO/EO/905 and the fee of $1700.00 is enclosed.

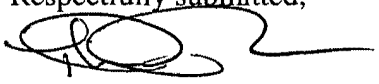
The Commissioner is authorized to charge payment of the following fees associated with this communication or credit any overpayment to Deposit Account No. 19-4375.

XXX Any additional filing fees required under 37 CFR §1.16.

XXX Any patent application processing fees under 37 CFR §1.17.

Issuance of the official Filing Receipt is respectfully solicited.

Respectfully submitted,



TPP:mat
Attorney Docket No.: TPP 31753

Thomas P. Pavelko
Registration No. 31,689

STEVENS, DAVIS, MILLER & MOSHER, L.L.P.
1615 L Street, N.W., Suite 850
Washington, D.C. 20036
Telephone: (202) 785-0100
Facsimile: (202) 408-5200 or (202) 408-5088
Date: July 6, 2005

FORM PTO-1390 (Modified) U.S. PATENT AND TRADEMARK OFFICE; U.S. DEPARTMENT OF COMMERCE
(REV. 2-2005)

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A SUBMISSION UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: TPP 31

U.S. APPLICATION NO. (If known, see 37 CFR 1.5): 10/518,016

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/GB02/02557	13 June 2003	14 June 2002

TITLE OF INVENTION
COMBINATION OF AZELASTINE AND STEROIDS

APPLICANT(S) FOR DO/EO/US
Amar LULLA
Geena MALHOTRA

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

1. ☐ This is a **FIRST** submission of items concerning a submission under 35 U.S.C. 371.
2. ☒ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a submission under 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 (24) indicated below.
4. ☐ The US has been elected (Article 31).
5. ☐ 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. ☐ 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. ☐ 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. ☐ 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)).
11. ☐ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☐ A copy of the International Search Report (PCT/ISA/210).

Items 13 to 23 below concern document(s) or information included:

13. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☒ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☐ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A power of attorney and/or change of address letter.
19. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13*ter*.2 and 37 CFR 1.821 - 1.825.
20. ☐ A second copy of the published International Application under 35 U.S.C. 154(d)(4).
21. ☐ A second copy of the English language translation of the International Application under 35 U.S.C. 154(d)(4).
22. ☐ Express Mail Label No.
23. ☒ Other items or information:

Response to Notification Concerning Missing Requirements

UNITED STATES PATENT AND TRADEMARK OFFICE

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

U.S. APPLICATION NUMBER NO.	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
10/518,016	Amar Lulla	TPP31753

INTERNATIONAL APPLICATION NO.	
PCT/GB03/02557	
I.A. FILING DATE	PRIORITY DATE
06/13/2003	06/14/2002

Thomas P Pavelko
Stevens Davis Miller & Mosher
1615 L Street N W
Suite 850
Washington, DC 20036

RESPONSE DUE 7-9-05
DOCKETED DATE 5-11-05
BY GB

CONFIRMATION NO. 4912
371 FORMALITIES LETTER

OC000000015966219

Date Mailed: 05/09/2005

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 a Designated / Elected Office (37 CFR 1.495).

- Copy of the International Application filed on 12/14/2004
- Copy of the International Search Report filed on 12/14/2004
- Copy of IPE Report filed on 12/14/2004
- Preliminary Amendments filed on 12/14/2004
- U.S. Basic National Fees filed on 12/14/2004
- Priority Documents filed on 12/14/2004

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.

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

SUMMARY OF FEES DUE:

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

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

ALL OF THE ITEMS SET FORTH ABOVE MUST BE SUBMITTED WITHIN TWO (2) MONTHS FROM THE DATE OF THIS NOTICE OR BY 32 MONTHS 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).

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.*

FRANCINE YOUNG

Telephone: (703) 308-9140 EXT 215

PART 1 - ATTORNEY/APPLICANT COPY

U.S. APPLICATION NUMBER NO.	INTERNATIONAL APPLICATION NO.	ATTY. DOCKET NO.
10/518,016	PCT/GB03/02557	TPP31753

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of

Amar LULLA et al

Group Art Unit: Unassigned

Serial No.: 10/518,016

Examiner: Unassigned

Filed: December 14, 2004

Confirmation No. 4912

For: COMBINATION OF AZELASTINE AND STEROIDS

INFORMATION DISCLOSURE STATEMENT

Commissioner of Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

Pursuant to Rules 56 and 98, Applicants hereby call the attention of the Patent Office to the references listed on the attached Form PTO 1449. These references were cited in an International Search Report issued in connection with the corresponding international application.

Applicants present these references so that the Patent Office may, in the first instance, determine any relevancy thereof to the presently claimed invention, see Beckman Instruments, Inc. v. Chemtronics, Inc., 439 F.2d 1369, 1380, 165 USPQ 355, 364 (5th Cir. 1970).

Applicants respectfully request that these references be expressly considered during the prosecution of this application and made of record herein and appear among the "References Cited" on any patent to issue herefrom.

Respectfully submitted,

TPP/mat
Attorney Docket No.: TPP 31753

Thomas P. Pavelko
Registration No. 31,689

STEVENS, DAVIS, MILLER & MOSHER, L.L.P.
1615 L Street, N.W., Suite 850
Washington, D.C. 20036
Telephone: (202) 785-0100
Facsimile: (202) 408-5200 or (202) 408-5088

Date: July 6, 2005

FORM PTO-1449 (Rev. 4/92) U.S. Department of Commerce Patent and Trademark Office	ATTY. DOCKET NO. TPP 31753	SERIAL NO. 10/518,016
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use several sheets if necessary)	APPLICANT Amar LULLA et al	
	FILING DATE December 14, 2004	GROUP Applications

U.S. PATENT DOCUMENTS

EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION	
							YES	NO
		9 7 0 1 3 3 7	01/97	WO				
		0 7 8 0 1 2 7	06/97	EP				

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

		Database Medline "Online! US National Library of Medicine (NLM), Bethesda, MD, US: 2000 Portmann D et al: "Acceptability of local treatment of allergic rhinitis with a combination of a corticoid (beclomethasone) and an antihistaminic (azelastine); vol. 121, no. 4, 2000, pages 273-279
		Busse W W et al: "Corticosteroid-Sparing Effect of Azelastine in the Management of Bronchial Asthma" - American Journal of Respiratory and Critical Care Medicine, American Lung Association, new York, NW, vol. 153, no. 1, 1996, pages 122-172, page 127, column 1, paragraph 2

EXAMINER	DATE CONSIDERED

EXAMINER: Initial if citation is considered, draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

(Form PTO-1449 [6-4])

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61K 31/435, 31/55, 31/445, 31/57 //
(A61K 31/57, 31:435, 31:445, 31:55)

A1

(11) International Publication Number: WO 97/01337

(43) International Publication Date: 16 January 1997 (16.01.97)

(21) International Application Number: PCT/US96/10789

(22) International Filing Date: 25 June 1996 (25.06.96)

(30) Priority Data:
08/496,814 29 June 1995 (29.06.95) US

(71) Applicant: McNEIL-PPC, INC. [US/US]; 7050 Camp Hill Road, Fort Washington, PA 19034 (US).

(72) Inventor: HELZNER, Eileen; 505 Anthony Drive, Plymouth, PA 19462 (US).

(74) Agents: CIAMPORCERO, Audley, A. et al.; Johnson and Johnson, One Johnson & Johnson Plaza, New Brunswick, NJ 08933-7003 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, 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 the receipt of amendments.

(54) Title: THE COMBINATION OF TOPICAL NASAL ANTIHISTAMINES AND TOPICAL NASAL STEROIDS

(57) Abstract

Nasal spray or nasal drops for the treatment of allergic rhinitis are disclosed comprising: a) an effective amount of a topical antihistamine to relieve histamine mediated symptoms where said topical nasal antihistamine is selected from the group consisting of levocabastine, azelastine and azatadine; b) an effective amount of a topical nasal steroid to reduce inflammation where said nasal steroid is selected from the group consisting of beclomethasone, flunisolide, triamcinolone, dexamethasone and budesonide; and c) sterile water.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	**GB**	United Kingdom	**MW**	Malawi
AT	Austria	**GE**	Georgia	**MX**	Mexico
AU	Australia	**GN**	Guinea	**NE**	Niger
BB	Barbados	**GR**	Greece	**NL**	Netherlands
BE	Belgium	**HU**	Hungary	**NO**	Norway
BF	Burkina Faso	**IE**	Ireland	**NZ**	New Zealand
BG	Bulgaria	**IT**	Italy	**PL**	Poland
BJ	Benin	**JP**	Japan	**PT**	Portugal
BR	Brazil	**KE**	Kenya	**RO**	Romania
BY	Belarus	**KG**	Kyrgystan	**RU**	Russian Federation
CA	Canada	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CF	Central African Republic			**SE**	Sweden
CG	Congo	**KR**	Republic of Korea	**SG**	Singapore
CH	Switzerland	**KZ**	Kazakhstan	**SI**	Slovenia
CI	Côte d'Ivoire	**LI**	Liechtenstein	**SK**	Slovakia
CM	Cameroon	**LK**	Sri Lanka	**SN**	Senegal
CN	China	**LR**	Liberia	**SZ**	Swaziland
CS	Czechoslovakia	**LT**	Lithuania	**TD**	Chad
CZ	Czech Republic	**LU**	Luxembourg	**TG**	Togo
DE	Germany	**LV**	Latvia	**TJ**	Tajikistan
DK	Denmark	**MC**	Monaco	**TT**	Trinidad and Tobago
EE	Estonia	**MD**	Republic of Moldova	**UA**	Ukraine
ES	Spain	**MG**	Madagascar	**UG**	Uganda
FI	Finland	**ML**	Mali	**US**	United States of America
FR	France	**MN**	Mongolia	**UZ**	Uzbekistan
GA	Gabon	**MR**	Mauritania	**VN**	Viet Nam

THE COMBINATION OF TOPICAL NASAL ANTIHISTAMINES AND TOPICAL NASAL STEROIDS

The present invention relates to prevention and treatment of the symptoms of seasonal and perennial allergic rhinitis. More particularly, the present invention relates to the prevention and treatment of the symptoms of seasonal and perennial allergic rhinitis by the application of a combination of topical nasal antihistamines and topical nasal steroids.

BACKGROUND OF THE INVENTION

Seasonal allergic rhinitis is most frequently caused by pollen, pollen fragments and mold spores. The airborne pollens, pollen fragments and mold spores are deposited on the nasal mucosa. In sensitive individuals, rhinitis symptoms develop which include puffy, sore eyes, sneezing, nasal congestion, sinus headaches and fatigue.

The chronic symptoms of perennial allergic rhinitis are most frequently caused by reaction to perennial allergens, such as, house dust mite, mold, cockroach, animal saliva, urine, and dander. The symptoms resemble those of seasonal allergic rhinitis but the duration is year round or episodic depending upon the source of the allergens.

Antihistamines are the primary medicaments employed to treat allergic rhinitis. Antihistamines are helpful to control sneezing, itching, and rhinorrhea as well as associated ocular symptoms but are ineffective in relieving nasal blockage. Antihistamines compete with histamine for binding to H_1 receptors and thereby prevent the action of histamine which includes bronchospasm, edema, increased mucus secretion and itching.

The antihistamines primarily in use today are orally active and administered. However, intranasally (topically) administered antihistamines, including azelastine and levocabastine have also been shown to be useful antihistamines in the treatment of allergic rhinitis. The intranasally administered antihistamines have a quick onset of action because they are delivered directly to the site of activity.

Also employed to treat allergic rhinitis are nasal steroids, particularly the corticosteroids. Such steroids have powerful effects on immunologic and hormonal processes and are very effective in treating the inflammation which accompanies the allergic reaction. Suitable nasal steroids known in use today include beclamethasone, flunisolide, triamcinolone, dexamethasone and budesonide.

SUMMARY OF THE INVENTION

There is provided by the present invention a nasal spray or nasal drops for the treatment of allergic rhinitis comprising:

a) an effective amount of a topical antihistamine to relieve histamine mediated symptoms where said topical nasal antihistamine is selected from the group consisting of levocabastine, azelastine and azatadine;

b) an effective amount of a topical nasal steroid to reduce inflammation where said nasal steroid is selected from the group consisting of beclomethasone, flunisolide, triamcinolone, dexamethasone and budesonide; and

c) sterile water.

DETAILED DESCRIPTION OF THE INVENTION

The topical antihistamines herein are potent H^1 receptor antagonists which relieve the histamine mediated symptoms, i.e. sneezing, runny nose, itchy nose, etc. The H^1 receptor antagonists block the receptor sites and thereby block the expression of the histamine effect. Thus, persons skilled in the art understand that only a sufficient amount of the antihistamine should be administered to relieve histamine mediated symptoms and no more. This amount will vary depending on whether levocabastine, azelastine or azatadine is employed. In the case of levocabastine from about 0.05 to about 10 mg and preferably from about 0.5 to about 5 mg should be administered in this combination every 4 to 12 hours. In the case of azelastine from about 0.05 to about 10 mg and preferably from about 0.5 to about 5 mg should be administered in this combination every 4 to 12 hours. In the case of azatadine, from about 0.05 to about 10 and preferably from about 0.5 to about

5 mg should be administered in this combination every 4 to 12 hours. To achieve these dosage ranges, levocabastine should constitute of the nasal spray or nasal drops composition from about 0.2 to about 40 mg/ml and preferably from about 2 to about 20 mg/ml. To achieve these dosage ranges, azelastine should constitute of the nasal spray or nasal drops composition from about 0.2 to about 40 mg/ml and preferably from about 2 to about 20 mg/ml. Similarly, azatadine should constitute from about 0.2 to about 40 mg/ml and preferably from about 2 to about 20 mg/ml.

Levocabastine as used herein includes levocabastine and its pharmaceutically acceptable acid addition salts. Suitable salts include the hydrochloric, hydrobromic, sulfuric, nitric, acetic, propionic, butanedioic, etc. salts. The preferred salt is hydrochloric. Levocabastine, (-)-[3S-1(cis),3,4]-1-[4-cyano-4-(4-fluorophenyl)cyclohexyl]-3-methyl-4-phenyl-4-piperidine carboxylic acid, is a well known compound and may be prepared by the method of U.S. Pat. 4,369,184, EP 34,415 or Stokbroekx, R. A., et al., *Drug Dev. Res.* 8: 87-93 (1986).

Azelastine as used herein, includes azelastine and its pharmacutically acceptable salts. Preferred are the acid addition salts, such as, the hydrohalo salts and salts with organic acids. Preferred salts include hydrochloridic hydrobromidic, embonic acid, maleic acid, citric acid and tartaric acid salts. Azelastine, 4-(p-chlorobenzyl)-2-[N-methyl-perhydroazepin-4-yl)-1-(2H)-phthalazinone, is a well known compound and may be prepared according to Belg. Pat. 778,269; Vogelsang et al., U.S. Pat. 3,813,384 and Scheffler et al., Arch. Pharm. 321, 205 (1988).

Azatadine as used herein includes azatadine and its pharmaceutically acceptable salts. Preferred salts of azatadine include its maleate, sulfate, succinate and acetate salts. Aztadine, 4-aza-5-(N-methyl-4-piperidinylidene)-10,11-dinydro-5H-dibenzo[a,d]cycloheptene, is a well known compound and may be prepared according to Belg. Pat. 647,043; U.S. Pat. 3,3577,986 and Villani et al., J. Med. Chem. 15, 750 (1972).

The topical nasal steroids for use herein are corticosteroids which inhibit the release of mediators for the symptoms associated with allergic rhinitis from mast cells and basophils. They also reduce inflammation and

suppress neutrophil chemotaxis. The topical nasal steroids herein have relatively few side effects but are known to cause nasal irritation, drying and epistaxis with use of nasal sprays. Thus, persons skilled in the art understand that only a sufficient amount of nasal steroid should be administered to inhibit mast cell mediator release and inflammation and no more. This amount will vary depending on whether beclomethasone, flunisolide, triamcinolone, dexamethasone or budesonide is employed. Further, the nasal steroids are relatively long acting and alone can be administered once or twice daily. However, when used in conjunction with an active ingredient requiring more frequent administration, the amount of nasal steroid must be adjusted accordingly. For beclomethasone, from about 10 to about 100 mcg, and preferably from about 15 to about 85 mcg should be administered in this combination every 4 to 12 hours. To achieve these dosage ranges, the beclomethasone should constitute of the nasal spray or nasal drops composition from about 0.05 to about 0.5 mg/ml, and preferably from about 0.1 to about 0.3 mg/ml. For flunisolide, from about 30 to about 300 mcg, and preferably from about 50 to about 200 mcg should be administered in this combination every 4 to 12 hours. To achieve these dosage ranges, the flunisolide should constitute of the nasal spray or nasal drops composition from about 0.1 to about 1.0 mg/ml, and preferably from about 0.15 to about 0.5 mg/ml. For triamcinolone, from about 10 to about 100 mcg, and preferably from about 15 to about 85 mcg should be administered in this combination every 4 to 12 hours. To achieve these dosage ranges, the triamcinolone should constitute of the nasal spray or nasal drops composition from about 0.05 to about 0.5 mg/ml, and preferably from about 0.1 to about 0.3 mg/ml. For dexamethasone, from about 40 to about 400 mcg, and preferably from about 60 to about 340 mcg should be administered in this combination every 4 to 12 hours. To achieve these dosage ranges, the dexamethasone should constitute of the nasal spray or nasal drops composition from about 0.2 to about 2.0 mg/ml, and preferably from about 0.4 to about 1.2 mg/ml. For budesonide, from about 40 to about 400 mcg, and preferably from about 60 to about 340 mcg should be administered in this combination every 4 to 12 hours. To achieve these dosage ranges, the budesonide should constitute of the nasal spray or nasal drops composition from about 0.2 to about 2.0 mg/ml, and preferably from about 0.4 to about 1.2 mg/ml.

The corticosteroid topical nasal steroids are, as a general matter, poorly soluble in water. Thus, they are administered in particulate form, as a micronized suspension in a suitable carrier/solvent system. For the treatment of the lung, it is desirable to produce aerosol particle sizes of less than 3 microns. However, in the instant case where it is desirable to treat nasal symptoms, the necessity of producing an aerosol of small particles is removed. For the present invention, it is only necessary to create a stable suspension of the corticosteroid in water which can be delivered by drops or spray directly into the nasal passages. The particle size of the corticosteroid in suspension is not critical so long as the particle is small enough that the amount of compound available for therapeutic activity is not surface area limited and the particle is stable in suspension. The suspension may be maintained with suitable liposomes. Preferably, however, the suspension is maintained by use of solubilizing agents and a suitable surfactant. Solubilizing agents herein include 1,2-propane diol, 1,3-propane diol, polyethylene glycol having a molecular weight of 100 to 800, dipropylene glycol, or ethanol. A suitable surfactant may be a pharmaceutically acceptable non-ionic, anionic or cationic surfactant. Examples of suitable non-ionic surfactants include glycerol fatty acid esters such as glycerol monostearate, glycol fatty acid esters such as propylene glycol monostearate, polyhydric alcohol fatty acid esters such as polyethylene glycol (400) monooleate, polyoxyethylene fatty acid esters such as polyoxyethylene (40) stearate, polyoxyethylene fatty alcohol ethers such as polyoxyethylene (20) stearyl ether, polyoxyethylene sorbitan fatty acid esters such as polyoxyethylene sorbitan monostearate or polysorbate 20, fatty acid ethanolamides and their derivatives such as the diethanolamide of stearic acid, and the like. Examples of suitable anionic surfactants are soaps including alkali soaps, such as sodium, potassium and ammonium salts of aliphatic carboxylic acids, usually a fatty acids, such as sodium stearate. Organic amine soaps, also included, include organic amine salts of aliphatic carboxylic acids, usually fatty acids, such as triethanolamine stearate. Another class of suitable soaps is the metallic soaps, salts of polyvalent metals and aliphatic carboxylic acids, usually fatty acids, such as aluminum stearate. Examples of suitable cationic surfactants include amine salts such as octadecyl ammonium chloride, quarternary ammonium compounds such as benzalkonium chloride. Other examples of these and other suitable surfactants can be found in "Pharmaceutical Emulsions and Emulsifying Agents" by Lawrence M. Spatton, second edition; The Chemist and Druggist,

London; "Emulsions' Theory and Practice" by Paul Becher, Reinhold Publishing Corporation, New York; and "Detergents and Emulsifyers, 1969 Annual" by John M. McCutcheon, Morristown, N.J., the disclosures thereof being incorporated herein by reference.

Only sufficient solubilizing agent and surfactant should be employed to stabilize the suspension/emulsion. Generally there should be employed from about 5 to about 30% w/v and preferably from 10 to about 25% w/v of cosolvent. Likewise, there should be employed from about 0.1 to about 10% w/v and preferably from about 0.5 to about 5% w/v of surfactant.

Beclamethasone as used herein includes beclamethasone, beclamethasone acetate, beclamethasone valerate, beclamethasone propionate, beclamethasone dipropionate and the like, including the hydrates thereof. Beclamethose, 9-chloro-11,17,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione, may be obtained commercially and is prepared according to Brit. Pat. 912,378 and Brit. Pat. 901,093. Beclamethasone is commercially available.

Flunisolide as used herein includes flunisolide and flunisolide acetate and hydrates thereof. Flunisolide, 6-fluoro-11,21-dihydroxy-16,17-[(1-methylethylidene)bis(oxy)]pregna-1,4-diene-3,20-dione, may be prepared using *S. roseochromogenes* as in Brit. Pat. 933,867 and Chem. Abst. 60, 3070f (1964) or using *Cunninghamella blakesleeana* as in U.S. pat. 3,124,571. Flunisolide is also prepared in 4,273,710. Flunisolide is commercially available.

Triamcinolone as used herein includes triamcinolone and its 16-α, 21-diacetate; triamcinolone acetonide, and its 21-acetate, 21-disodium phosphate, and 21-hemisuccinate; triamcinolone benetonide and triamcinolone hexacetonide, including hydrates thereof. Triamcinolene, 9-fluoro-11,16,17,21-tetrahydroxypregna-1,4-diene-3,20-dione, may be prepared according to Bernstein et al., *J. Am. Chem. Soc.* 78, 5693 (1956) and 81, 1689 (1959); Thoma et al., *J. Am. Chem. Soc.* 79, 4818 (1957); U.S. Pat. 2,789,118 or U.S. Pat. 3,021,347. Triamcinolone acetonide may be prepared by stirring a suspension of triamcinolone in acetone in the presence of a trace of perchloric acid. Triamcinolone benetonide may be prepared according to Ger. Pat. 2,047,218 or U.S. Pat. 3,749,712. Triamcinolone

hexacetonide may be prepared according to U.S. pat. 3,457,348. The triamcinolone and derivatives as taught herein have been sold or are available commercially.

Dexamethasone as used herein includes dexamethasone and its 21-phosphate, 21-acetate, 21-phosphate disodium salt, 21-dimethylaminoacetate, 21-isonicotinate, 17,21-dipropionate and 21-palmitate. Dexamethasone, (11ß, 16α)-9-fluoro-11,17,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione, may be prepared according to Arth et al., *J. Am. Chem. Soc.* 80, 3161 (1958); Oliveto et al., J. Am. Chem. Soc. 80, 4431 (1958); U.S. Pat. 3,007,923; Ger. Pat. 1,113,690 or Brit. Pat. 869,511. Dexamethasone is commercially available.

Budesonide as used herein includes budesonide and its pharmaceutically acceptable salts. Preferred salts of budesonide include its palmitate, laurate, myristate, stearate, oleate, valerate and acetate salts. Budesonide, 16,17-butylidenebis(oxy)-11,21-dihydroxypregna-1,4-diene-3,20-dione, is a well known compound and may be prepared according to U.S. Pat. No. 3,929,768, GB Pat. No. 1,429,922, or A. Thalen, R. L. Brattsand, Arzneimittel Forsch. 29, 1787 (1979).

The nasal spray or nasal drop formulation herein can contain, in addition to the compounds discussed above antimicrobial agents, antioxidants, agents to increase viscosity, isotonic agents, buffers, solubilizing agents, surface active agents and the like. Suitable antimicrobial agents include chlorobutanol, phenylmercuric nitrate, phenyl ethyl alcohol, thimerosal, the quaternary ammonium germicides, such as, benzalkonium chloride, benzethonium chloride or cetylpyridium chloride. Suitable antioxidants include sodium sulfite, sodium ascorbate, oxime sulfate, etc. The preferred isotonic agent is sodium chloride however, other isotonic agents such as dextrose, boric acid and sodium tartrate may be employed. The object of the buffer is to adjust the pH to one compatible with nasal mucous membranes and to stabilize the active ingredient. Ideally the target pH should vary between about 4 and about 6.5. Suitable buffers included phthalate buffers, borate buffers, phosphate buffers, such as $HPO_4^{2-}/H_2PO_4^-$, acetate buffers, such as acetic acid/sodium acetate, a bicarbonate buffer such as CO_2/HCO_3, or a citrate buffer, such as citric acid/citrate, also it may be

adjusted by simply adding an acid such as HCl to achieve the desired acidity. Suitable agents to increase viscosity include polyvinyl alcohol, cellulose derivatives, polyvinylpyrollidone, polysorbates or glycerine. Suitable surface active agents improve absorption by the nasal mucosa and include polyoxyl 40 stearate, polyoxyethylene 50 stearate, polysorbate 80 and octoxynol.

In general, the concentration of the additives will be in the range as follows:

Additive	% W/V
antimicrobial agent	0.001 - 2.0
antioxidant	0.01 - 0.20
isotonic agent	0.01 - 0.50
solubilizing agents	0.01 - 1.0
viscosity builders	0.1 - 2.0
surface active agents	0.01 - 1.0

The buffer should be added in sufficient amount to achieve the pH range stated above of about 4.0 to about 6.5.

Aerosol formulations and nose drops are prepared as per known techniques. The water employed should be of an appropriate pharmacutical grade of purified water. These formulations should be administered by drop or spray every 4 to 6 hours to obtain the desired relief.

WHAT IS CLAIMED IS:

1. A nasal spray or nasal drops formulation comprising:

a) an effective amount of a topical antihistamine to relieve histamine mediated symptoms where said topical nasal antihistamine is selected from the group consisting of levocabastine, azelastine and azatadine;

b) an effective amount of a topical nasal steroid to reduce inflammation where said nasal steroid is selected from the group consisting of beclomethasone, flunisolide, triamcinolone, dexamethasone and budesonide; and

c) sterile water.

2. The formulation of claim 1 wherein said topical nasal antihistamine is levocabastine and said topical nasal steroid is selected from the group consisting of beclomethasone, flunisolide, triamcinolone, dexamethasone and budesonide.

3. The formulation of claim 1 wherein said topical nasal antihistamine is azelastine and said topical nasal steroid is selected from the group consisting of beclomethasone, flunisolide, triamcinolone, dexamethasone and budesonide.

4. The formulation of claim 1 wherein said topical nasal antihistamine is azatadine and said topical nasal steroid is selected from the group consisting of beclomethasone, flunisolide, triamcinolone, dexamethasone and budesonide.

5. The formulation of claim 1 wherein said levocabastine constitutes of the nasal spray or nasal drops composition from about 0.2 to about 40 mg/ml; said azelastine constitutes of the nasal spray or nasal drops composition from about 0.2 to about 40 mg/ml; and said azatadine constitutes of the nasal spray or nasal drops composition from about 0.2 to about 40 mg/ml.

6. The formulation of claim 1 wherein said beclomethasone constitutes of the nasal spray or nasal drops composition from about 0.05 to about 0.5

mg/ml; said flunisolide constitutes of the nasal spray or nasal drops composition from about 0.1 to about 1.0 mg/ml; said triamcinolone constitutes of the nasal spray or nasal drops composition from about 0.05 to about 0.5 mg/ml; said dexamethasone constitutes of the nasal spray or nasal drops composition from about 0.2 to about 2.0 mg/ml; and said budesonide constitutes of the nasal spray or nasal drops composition from about 0.2 to about 2.0 mg/ml.

INTERNATIONAL SEARCH REPORT

International Application No
[redacted]US 96/10789

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/435 A61K31/55 A61K31/445 A61K31/57 //(A61K31/57, 31:435,31:445,31:55)

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.
X	DRUGS, vol. 45, no. 4, 1993, pages 518-527, XP000603981 HORAK F.: "SEASONAL ALLERGIC RHINITIS" see abstract see page 521, left-hand column, line 8 - page 522, left-hand column, line 41 see page 526, right-hand column, line 1 - line 15 --- -/--	1-6

[X] Further documents are listed in the continuation of box C. [ ] 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
29 October 1996	14. 11. 96

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	Economou, D

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

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CLINICAL PHARMACY, vol. 8, no. 7, July 1989, pages 474-485, XP000603999 DELAFUENTE J.C., ET AL.: "PHARMACOTHERAPY OF ALLERGIC RHINITIS" see abstract see page 477; table 1 see page 479, left-hand column, line 13 - page 481, left-hand column, line 35 see page 482, left-hand column, paragraph 3 see page 483, left-hand column, paragraph 2 - paragraph 3 ---	1-6
Y	J.ALLERGY CLIN. IMMUNOL., vol. 82, no. 5, November 1988, pages 890-900, XP000603998 BUSSE W.: "NEW DIRECTIONS AND DIMENSIONS IN THE TREATMENT OF ALLERGIC RHINITIS" see page 890, left-hand column, paragraph 1 see page 892; table II see page 891, right-hand column, paragraph 4 - page 897, right-hand column, paragraph 2 see page 898, right-hand column, paragraph 1 see page 899, left-hand column, paragraph 2 ---	1-6
Y	CLINICAL IMMUNOTHERAPEUTICS, vol. 4, no. 4, April 1995, pages 270-278, XP000604030 LUND V.: "PRACTICAL APPLICATION OF THE INTERNATIONAL CONSENSUS ON THE MANAGEMENT OF RHINITIS" see abstract see page 273, left-hand column, paragraph 2 - page 274, right-hand column, paragraph 3 see page 277; table V ---	1-6
P,Y	INTERNISTA, vol. 3, September 1995, pages 167-170, XP000604083 PURELLO D'AMBROSIO F., ET AL.: "LEVOCABASTINA VERSUS FLUNISOLIDE NEL TRATTAMENTO DELLA RINITE ALLERGICA PERENNE" see abstract see page 168, left-hand column, line 5 - line 39 see page 168, right-hand column, last paragraph - page 169, left-hand column, line 6 --- -/--	1-6

1

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	HOSPITAL PRACTICE, vol. 31, no. 6, 15 June 1996, pages 61-73, XP000604174 HOLLINGSWORTH: "ALLERGIC RHINOCONJUCTIVITIS: CURRENT THERAPY" see page 67, middle column, paragraph 2 - page 71, middle column, paragraph 3 see page 67; table 4 ---	1-6
P,Y	ACTA OTORHINOLARYNGOL. , vol. 50, no. 1, January 1996, pages 25-32, XP000604028 WANG D., ET AL.: "THE ACTIVITY OF RECENT ANTI-ALLERGIC DRUGS IN THE TREATMENT OF SEASONAL ALLERGIC RHINITIS" see abstract see page 25, right-hand column, line 1 - line 4 see page 26, right-hand column, line 3 - line 13 see page 28, left-hand column, paragraph 2 - paragraph 4 see page 28, right-hand column, paragraph 3 - page 29, left-hand column, paragraph 2 see page 29, right-hand column, paragraph 1 - paragraph 2 see page 30, right-hand column, paragraph 2 - page 31, right-hand column, paragraph 1	1-6
Y	& MEETING OF THE ROYAL BELGIAN SOCIETY FOR ENT, HEAD AND NECK SURGERY, February 1995, BRUSSELS, -----	1-6

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 780 127 A1

(12) EUROPEAN PATENT APPLICATION

(43) Date of publication:
25.06.1997 Bulletin 1997/26

(21) Application number: **96308852.1**

(22) Date of filing: **05.12.1996**

(51) Int Cl.[6]: **A61K 31/57**, A61K 31/58, A61K 31/56, A61K 31/495, A61K 31/445, A61K 31/55 // (A61K31/56, 31:495), (A61K31/56, 31:445), (A61K31/56, 31:55), (A61K31/57, 31:495), (A61K31/57, 31:445), (A61K31/57, 31:55), (A61K31/58, 31:495), (A61K31/58, 31:445)

(84) Designated Contracting States:
AT BE CH DE DK ES FI FR GB GR IE IT LI LU NL PT SE

(30) Priority: **19.12.1995 US 574791**

(71) Applicant: **THE PROCTER & GAMBLE COMPANY**
Cincinnati, Ohio 45202 (US)

(72) Inventor: **Cramer, Ronald Dean**
Cincinnati, Ohio 45215 (US)

(74) Representative: **Woof, Victoria**
Procter & Gamble Pharmaceuticals Ltd.,
Patent Department,
Lovett House,
Lovett Road
Staines, Middlesex TW18 3AZ (GB)

(54) A nasal spray containing a steroid and a antihistamine

(57) The present invention relates to novel nasal spray compositions comprising a safe and effective amount of a glucocorticosteroid and an antihistamine possessing leukotriene inhibiting properties.

EP 0 780 127 A1

Printed by Jouve, 75001 PARIS (FR)

Description

TECHNICAL FIELD

The present invention relates to novel nasal spray compositions comprising a safe and effective amount of a glucocorticosteroid and an antihistamine.

BACKGROUND OF THE INVENTION

Allergic disorders remain a leading cause of both acute and chronic illnesses the world over. These illnesses are often times present in the form of acute or chronic rhinoconjunctivitis. The symptoms of allergic rhinoconjunctivitis are reddening of the eyes, ocular secretions, nasal congestion, ocular and palatial irritation, sneezing and hypersecretion. These symptoms occur following exposure to allergens. The most common allergens are grass and/or tree pollens, hence, allergic rhinoconjunctivitis is most common during the spring and summer months.

The symptoms of allergic rhinoconjunctivitis are believed to be due primarily to the stimulation of H-1 receptors by histamine, followed by reflexive activation of parasympathetic nerves causing increases in nasal secretion and obstruction. Histamine is initially released from the tissue mast cells upon sensitization of the mast cells. This sensitization results when airborne allergens combine with specific IgE antibodies attached to mast cell membranes.

Antihistamines and/or decongestants have traditionally been the drugs of choice in treating allergic rhinoconjunctivitis. Other forms of therapy include the use of cromolyn sodium, hypertonic salt solutions or immunotherapy.

In addition, Hagen et al., U.S. Patent 4,767,612, discloses nasal corticosteroid therapy as an effective means of treating allergic rhinoconjunctivitis; and is herein incorporated by reference in its entirety. Notwithstanding the many disclosures in the area of allergic rhinoconjunctivitis, there is still a need for additional formulations which provide improved symptomatic relief with increased user acceptance and compliance.

The present inventor has found that by combining a nasal corticosteroid with a leukotriene inhibiting antihistamine, improved intranasal compositions result, providing improved relief of symptoms generally associated with either seasonal or perennial allergic rhinoconjunctivitis.

It is, therefore, an object of the present invention to provide pharmaceutical compositions having improved effectiveness in the treatment of symptoms generally associated with either seasonal or perennial allergic rhinoconjunctivitis.

A further object of the present invention is to provide a safe and effective method for treating the symptoms of seasonal or perennial allergic rhinoconjunctivitis.

These objects and other objects will become more apparent from the detailed description that follows.

SUMMARY OF THE INVENTION

The present invention relates to pharmaceutical compositions for nasal administration comprising:

a) a safe and effective amount of a glucocorticoid selected from the group consisting of beclomethasone, flunisolide, triamcinolone, fluticasone, mometasone, budesonide, pharmaceutically acceptable salts thereof and mixtures thereof;

b) a safe and effective amount of a leukotriene inhibiting antihistamine selected from the group consisting of cetirizine, loratadine, azelastine, pharmaceutically acceptable salts thereof, optically active racemates thereof and mixtures thereof; and

c.) an intranasal carrier.

The intranasal carrier of the present invention is preferably aqueous.

The present invention also relates to a method for the treatment of symptoms associated with seasonal or perennial allergic rhinoconjunctivitis comprising the administration of a safe and effective amount of the intranasal pharmaceutical compositions of the present invention. By "symptoms of seasonal or perennial allergic rhinoconjunctivitis" or "symptoms associated with seasonal or perennial allergic rhinoconjunctivitis," is meant ocular and palatial irritation, ocular secretions, reddening of the eyes, sneezing, mucoid hypersecretion, nasal congestion and itching.

By "safe and effective amount," as used herein, is an amount that is effective to mitigate and/or treat the symptoms for which the active ingredient is indicated in a human without undue adverse side effects commensurate with a reasonable risk/benefit ratio.

By "leukotriene inhibiting antihistamine,"as used herein, is meant an antihistamine effective in inhibiting or reducing *in vivo* the biosynthesis of and/or cellular release of leukotrienes or otherwise modulating mammalian leukotriene levels.

The pH of the compositions is preferably from about 4.5 to about 9, more preferably from about 6 to about 7.

All percentages and ratios herein are by weight unless otherwise specified. Additionally, all measurements are

made at 25°C unless otherwise specified.

DETAILED DESCRIPTION OF THE INVENTION

The compositions of the present invention contain the essential components as well as various optional components as indicated below.

More specifically, the compositions of the instant invention are for nasal administration and contain a therapeutically effective amount of the herein described pharmaceutical agents. They are preferably provided as isotonic aqueous solutions, suspensions or viscous compositions which may be buffered to a selected pH.

Essential Ingredients

Glucocorticoid Agents

Agents within this class have potent glucocorticoid activity and weak mineralocorticoid activity. Glucocorticoid agents most useful to the present invention include those selected from the group consisting of beclomethasone, flunisolide, triamcinolone, fluticasone, mometasone, budesonide, pharmaceutically acceptable salts thereof and mixtures thereof.

When used in the compositions of the present invention, the glucocorticoid component is preferably present at a concentration of from about 0.001% to about 0.2%, more preferably from about 0.01% to about 0.1%.

Leukotriene Inhibiting, Antihistaminic Agents

Antihistamines useful to the present invention are histamine H-1 receptor antagonists which also reduce mammalian leukotriene levels. Such H-1 receptor antihistamines may be selected from among the following groups of antihistamines: piperazines, phenothiazines, piperidines.

Examples of useful leukotriene inhibiting antihistamines include cetirizine, loratadine, azelastine and the like, optically active racemates thereof, pharmaceutically acceptable salts thereof and mixtures thereof. When used in the compositions of the present invention, the antihistamine component is preferably present at a concentration of from about 0.01% to about 4.0%, more preferably from about 0.01% to about 1%.

Pharmaceutically-Acceptable Aqueous Nasal Carrier.

One other essential component of the present invention is a pharmaceutically-acceptable intranasal carrier. Preferred for use herein are aqueous saline solution carriers. These solutions which generally contain sodium chloride as the salt are fully described in Remington's Pharmaceutical Sciences, 17th edition (1985) p. 835, which is herein incorporated by reference. The salt is present in the solution at a level of about 0.01% to about 2%, preferably from about 0.5% to about 1.0%.

The combination of any of the above described antihistamines and glucocorticoids can be conveniently administered nasally to warm-blooded animals to elicit the desired therapeutic response by formulating it into a nasal dosage form, together with a nontoxic pharmaceutically-acceptable nasal carrier. Suitable nontoxic pharmaceutically-acceptable nasal carriers are known to those skilled in the art and are also fully disclosed in Remington's Pharmaceutical Sciences, 17th edition, 1985. Obviously, the choice of suitable carrier forms will depend on the exact nature of the particular nasal dosage form required, e.g., whether the drug(s) is to be formulated into a nasal solution (for use as drops or as a spray), a nasal suspension, a nasal ointment, a nasal gel or another nasal form. Preferred nasal dosage forms are solutions, suspensions and gels, which normally contain sodium chloride in a major amount of water (preferably purified water) in addition to the antihistamine and glucocorticoid. Minor amounts of other ingredients such as pH adjusters (e.g., an acid such as HCl), emulsifiers or dispersing agents, buffering agents, preservatives, wetting agents and jelling agents (e.g., methylcellulose) may also be present. Most preferably, the nasal composition is isotonic, i.e., it has the same osmotic pressure as blood and lacrimal fluid.

Preferably the composition is applied to the nasal mucosa via topical application of a safe and effective amount of the composition to treat nasal symptoms. The amount of the antihistamine and glucocorticoid combination and frequency of topical application to the nasal mucosa may vary, depending upon personal or medical needs, but it is suggested, as an example, that topical application range from about once per day to about four times daily, preferably twice daily, most preferably once daily. As a practical matter the selected therapeutic compositions will normally be prepared in unit dosage forms or actuations to contain therapeutically effective amounts of the selected antihistamine and glucocorticoid combination. In specific instances fractions of these dosage units or multiple dosage units will be employed. Typically, dosage units may be prepared to deliver from about 0.5 mcg to about 100 mcg of the glucocorticoid

agent and from about 5 mcg to about 1000 mcg of the antihistaminic agent per spray actuation (e.g., 50 mg to about 200 mg of the spray composition). A typical dose contains one to four sprays per nostril.

Optional Ingredients

Optional ingredients useful in the present invention include decongestants. Decongestants useful to the present invention may be selected from among the class of sympathomimetic agents; examples of which include pseudoephedrine, desoxyephedrine, propylhexedrine, phenylpropanolamine, xylometazoline, phenylephrine, tetrahydrozoline, naphazoline, oxymetazoline, tramazoline and pharmaceutically acceptable salts thereof. Also useful as decongestants are the 5-(2-imidazolinylamino)benzimedazole compounds. Mixtures of these decongestants can also be used.

When used in the compositions of the present invention, the sympathomimetic agents may be incorporated at concentrations, preferably, of from about 0.01% to about 0.5%, more preferably from about 0.05% to about 0.1%.

The compositions of the present invention may also contain antiallergics. Suitable antiallergics include, but are not limited to, cromolyn, ketotifen, N-allyl-(dichloro-3, 4-benzyl)-2-methylamino-2-propanol-1, AP-582 (Pharmaprojects No. 3055-under investigation by Ariad Pharmaceuticals), Andolast, oxatamide and pharmaceutically-acceptable salts thereof. Mixtures of these antiallergics may also be used.

Similarly, mucolytics such as acetylcysteine and anticholinergics such as ipratropium bromide may also be used in the compositions of the present invention.

Also of optional use in the compositions of the present invention are nonopiate analgesics such as oxaprozin. The intranasal use of oxaprozin is described in Namiki et al., Studies on improvement of pharmaceutical preparations prescribed in hospitals. VI. oxaprozin nasal spray, Drug Design and Delivery 1988;2:pp. 311-321, herein incorporated by reference. Further examples of preferred nonopiate analgesics include, but are not limited to, acetaminophen, acetylsalicylic acid, ibuprofen, etodolac, fenbuprofen, fenoprofen, flurbiprofen, indomethacin, ketoprofen, naproxen, pharmaceutically-acceptable salts thereof, optically active racemates thereof and mixtures thereof. Still further examples of such drugs are disclosed in U.S. Patent No. 4,522,828, to Sunshine et al., issued June 11, 1985; this patent being incorporated herein by reference in its entirety.

Synthetic opiate analgesics such as butorphanol may also be incorporated into the compositions of the present invention. The intranasal use of butorphanol is described in Baumel, Migraine: A pharmacologic review with newer options and delivery modalities, Neurology 1994;44(supp):pp. s13-s17, herein incorporated by reference. Further examples of preferred synthetic opioid analgesics include alfentanil, buprenorphine, fentanyl, meperidine, methadone, nalbuphine, natrexone, propoxyphene, pentazocine, sufenanil, pharmaceutically-acceptable salts thereof and mixtures thereof.

Compounds commonly known as lipoxygenase inhibitors and receptor antagonists are also optionally useful in the compositions of the present invention. Suitable lipoxygenase inhibitors are described in U.S. Patent 4,873,259, to Summers et al., issued October 10 1989 and European Patent Application 318093, both of which are herein incorporated by reference. Lipoxygenase antagonists suitable for use in the present invention include Zafirlukast (Accolate, Zeneca).

Leukotriene receptor antagonists may also be incorporated into the compositions of the present invention. Suitable examples include, but are not limited to, experimental agents such as LY171883, Wy-45,911, LY163443, ONO-RS-411 and ONO-RS-347 and ICI 198,615. A more detailed discussion of leukotriene receptor antagonists is found in Fleisch, J. H., Development of Cysteinyl Leukotriene Receptor Antagonists, Vol. 12 Advances in Inflammation Research 173-189 (A. Lewis et al. ed. 1988), herein incorporated by reference in its entirety.

Various aromatic components (e.g., aldehydes and esters) may also be used. These aromatics include, for example, menthol, camphor, eucalyptol, benzaldehyde (cherry, almond); citral (lemon, lime); neral; decanal (orange, lemon); aldehyde C-8, aldehyde C-9 and aldehyde C-12 (citrus fruits); tolyl aldehyde (cherry, almond); 2,6-dimethyl-octanal (green fruit); and 2-dodecenal (citrus, mandarin). Additional aromatic components suitable for use in the present invention include those described in U.S. Patent 4,136,163 to Watson et al., U.S. Patent 4,459,425 to Amano et al., and U.S. Patent 4,230,688 to Rowsell et al.; all of which are herein incorporated by reference. Mixtures of these aromatics can also be used.

The desired isotonicity of the compositions of this invention may be accomplished using, for example, the sodium chloride already present, or other pharmaceutically-acceptable agents such as dextrose, boric acid, citric acid, sodium tartrate, sodium phosphate, potassium phosphate, propylene glycol or other inorganic or organic solutes or mixtures thereof. Sodium chloride is preferred particularly for buffers containing sodium ions. Further examples of sodium chloride equivalents are disclosed in Remington's Pharmaceutical Sciences pp. 1491-1497 (Alfonso Gennaro 18th ed. 1990).

Viscosity of the compositions may be maintained at the selected level using a pharmaceutically-acceptable thickening agent. Methyl cellulose is preferred because it is readily and economically available and is easy to work with. Other suitable thickening agents include, for example, xanthan gum, microcrystalline cellulose, carboxymethyl cellu-

lose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose, carboxyvinyl polymer, carbomer, and the like or pharmaceutical salts thereof. Mixtures of such thickening agents may also be used. The preferred concentration of the thickener will depend upon the agent selected. The important point is to use an amount which will achieve the selected viscosity. Viscous compositions are normally prepared from solutions by the addition of such thickening agents.

Preferred compositions within the scope of this invention will contain from about 0.01% to about 5% of a humectant to inhibit drying of the mucous membrane and to prevent irritation. Any of a variety of pharmaceutically-acceptable humectants can be employed including, for example sorbitol, propylene glycol, polyethylene glycol, glycerol or mixtures thereof. As with the thickeners, the concentration will vary with the selected agent, although the presence or absence of these agents, or their concentration is not an essential feature of the invention.

Enhanced absorption across the nasal membrane can be accomplished employing a therapeutically acceptable surfactant. Typical useful surfactants for these therapeutic compositions include polyoxyethylene derivatives of fatty acid partial esters of sorbitol anhydrides such as Polysorbate 80, Polyoxyl 40 Stearate, Polyoxylethylene 50 Stearate and Octoxynol, as well as Oxyethylated tertiary octyl phenol formaldehyde polymer (available from Sterling Organics as tyloxapol) or mixtures thereof. The usual concentration is from 0.5% to 10% based on the total weight.

A pharmaceutically-acceptable preservative is generally employed to increase the shelf life of the compositions of the present invention. Benzyl alcohol is suitable, although a variety of preservatives including, for example, parabens, phenylethyl alcohol, thimerosal, chlorobutanol, phenylmecuric acetate or benzalkonium chloride may also be employed. The most preferred preservative system for use herein comprises a combination of benzalkonium chloride, chlorhexidine gluconate and disodium EDTA. A suitable concentration of the preservative will be from 0.001% to 2% based on the total weight, although there may be appreciable variation depending upon the agent selected Mixtures of these preservatives may also be used.

Other Optional Components. A variety of additional ingredients may be added to the emulsion compositions of the present invention. These additional ingredients include various polymers for aiding the film-forming properties and substantivity of the formulation, antioxidants, and agents suitable for aesthetic purposes such as fragrances, pigments, and colorings.

The compositions can also contain low levels of insoluble ingredients added, for example for visual effect purposes, e.g. thermochromic liquid crystalline materials such as the microencapsulated cholesteryl esters and chiral nematic (nonsterol) based chemicals such as the (2-methylbutyl) phenyl 4-alkyl(oxy)benzoates available from Hallcrest, Glenview, Illinois 60025, U.S.A. Mixtures of these ingredients may also be used.

EXAMPLES

The following examples further describe and demonstrate embodiments within the scope of the present invention. The examples are given solely for the purpose of illustration and are not to be construed as limitations of the present invention, as many variations thereof are possible without departing from the spirit and scope of the invention.

Example I

The intranasally administered pharmaceutical composition of the present invention is prepared by combining the following components utilizing conventional mixing techniques similar to that described below.

Component	Wgt %
beclomethasone diproprionate, monohydrate	0.042
loratadine	0.200
avicel RC - 591[1]	1.200
dextrose	5.100
polysorbate 80	0.025
benzalkonium chloride	0.040
phenylethyl alcohol	0.250
distilled water	q.s. to vol.

[1] microcrystalline cellulose and sodium carboxymethyl cellulose, supplied by FMC corporation.

In an appropriately sized vessel, the dextrose, polysorbate 80 and benzalkonium chloride are added one at a time to water with mixing, allowing each to dissolve or completely disperse before adding the next. To this is added, with mixing, a premixed slurry of the avicel and water. Upon forming a uniform solution, the beclomethasone, loratadine

and phenylethyl alcohol are added. After all the ingredients are added, purified water is used to bring the batch to the appropriate weight.

Administration of approximately 0.4 grams of the composition is used for topical nasal application to provide relief from allergy or allergy-like symptoms.

Example II

The intranasally administered pharmaceutical composition of the present invention is prepared by combining the following components utilizing conventional mixing techniques similar to that described in Example I.

Component	Wgt %
flunisolide	0.025
cetirizine	0.200
propylene glycol	2.000
polyethylene glycol	1.000
sodium chloride	0.900
ethylenediamine tetraacetic acid	0.050
benzalkonium chloride	0.010
distilled water	q.s. to vol.

Administration of approximately 0.4 grams of the composition is used for topical nasal application to provide relief from allergy or allergy-like symptoms.

Example III

The intranasally administered pharmaceutical composition of the present invention is prepared by combining the following components utilizing conventional mixing techniques similar to that described in Example I.

Component	Wgt %
triamcinolone acetonide	0.050
azelastine HCl	0.070
polysorbate 80	0.050
glycerin	2.000
hydroxypropyl methyl cellulose	1.000
sodium chloride	0.900
ethylenediamine tetraacetic acid	0.050
benzalkonium chloride	0.020
distilled water	q.s. to vol.

Administration of approximately 0.4 grams of the composition is used for topical nasal application to provide relief from allergy or allergy-like symptoms. Additionally, substantially similar results are also obtained using, in whole or in part, equivalent amounts of other glucocorticoid agents such as fluticasone, mometasone, budesonide, pharmaceutically acceptable salts thereof and mixtures thereof. Furthermore, the above described compositions may also contain a decongestant such as pseudoephedrine, phenylpropanolamine, phenylephrine, tetrahydrozoline, naphazoline, oxymetazoline, tramazoline, 5-(2-imidazolinylamino)benzimedazoles, optically active racemates thereof, pharmaceutically acceptable salts thereof and mixtures thereof. Those skilled in the art will quickly realize other suitable ingredients, diluents and dosage forms (or readily ascertain such using routine experimentation) which may further be incorporated into the above compositions without departing from the scope and spirit of the present invention.

Claims

1. A pharmaceutical composition comprising:

   a) a safe and effective amount of a glucocorticoid selected from the group consisting of beclomethasone,

flunisolide, triamcinolone, fluticasone, mometasone, budesonide, pharmaceutically acceptable salts thereof and mixtures thereof;
b) a safe and effective amount of a leukotriene inhibiting antihistamine selected from the group consisting of cetirizine, loratadine, azelastine, pharmaceutically acceptable salts thereof, optically active racemates thereof and mixtures thereof; and
c.) an intranasal carrier.

2. A composition according to Claim 1 in the form of an isotonic aqueous solution

3. A composition according to Claim 1 or 2 wherein the glucocorticoid is selected from the group consisting of beclomethasone, budesonide, fluticasone and mixtures thereof.

4. A pharmaceutical composition according to any of Claims 1-3, which further comprises a sympathomimetic amine selected from the group consisting of pseudoephedrine, desoxyephedrine, propylhexedrine, phenylpropanolamine, xylometazoline, phenylephrine, tetrahydrozoline, naphazoline, oxymetazoline, tramazoline, 5-(2-imidazolinylamino)benzimedazoles, pharmaceutically acceptable salts thereof, optically active racemates thereof and mixtures thereof.

5. A pharmaceutical composition according to any of Claims 1-4, which further comprises a non-steroidal anti inflammatory agent, or optically active racemates thereof and mixtures thereof.

6. A pharmaceutical composition according to any of Claims 1-5, which further comprises a lipoxygenase inhibitor or antagonist, a leukotriene receptor antagonist, a nonopiate analgesic, a mucolytic, an antiallergic, and pharmaceutically acceptable salts thereof and mixtures thereof.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 96 30 8852

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
Y	EP 0 605 203 A (SENJU PHARMA CO) 6 July 1994 * the whole document * -----	1-6	(A61K31/58, A61K31:495), (A61K31/58, A61K31:445)

TECHNICAL FIELDS SEARCHED (Int.Cl.6)

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
MUNICH	1 April 1997	Herrera, S

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)

UNITED STATES PATENT AND TRADEMARK OFFICE

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

U.S. APPLICATION NUMBER NO.	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
10/518,016	Amar Lulla	TPP31753

INTERNATIONAL APPLICATION NO.	
PCT/GB03/02557	
I.A. FILING DATE	PRIORITY DATE
06/13/2003	06/14/2002

Thomas P Pavelko
Stevens Davis Miller & Mosher
1615 L Street N W
Suite 850
Washington, DC 20036

CONFIRMATION NO. 4912

371 FORMALITIES LETTER

OC000000015966219

Date Mailed: 05/09/2005

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 a Designated / Elected Office (37 CFR 1.495).

- Copy of the International Application filed on 12/14/2004
- Copy of the International Search Report filed on 12/14/2004
- Copy of IPE Report filed on 12/14/2004
- Preliminary Amendments filed on 12/14/2004
- U.S. Basic National Fees filed on 12/14/2004
- Priority Documents filed on 12/14/2004

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.

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

SUMMARY OF FEES DUE:

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

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

ALL OF THE ITEMS SET FORTH ABOVE MUST BE SUBMITTED WITHIN TWO (2) MONTHS FROM THE DATE OF THIS NOTICE OR BY 32 MONTHS 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).

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.*

FRANCINE YOUNG

Telephone: (703) 308-9140 EXT 215

PART 2 - OFFICE COPY

U.S. APPLICATION NUMBER NO.	INTERNATIONAL APPLICATION NO.	ATTY. DOCKET NO.
10/518,016	PCT/GB03/02557	TPP31753

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

FORM PTO-1390 (Modified) (REV. 07-2004) U.S. PATENT AND TRADEMARK OFFICE; U.S. DEPARTMENT OF COMMERCE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A SUBMISSION UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	U.S. APPLICATION NO. (If known, see 37 CFR 1.5)
TPP31753	10/518016

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/GB03/02557	13 June 2003	14 June 2002

TITLE OF INVENTION
COMBINATION OF AZELASTINE AND STEROIDS

APPLICANT(S) FOR DO/EO/US
Amar LULLA
Geena MALHORTRA

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

1. ☒ This is a **FIRST** submission of items concerning a submission under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a submission under 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 (24) indicated below.
4. ☒ The US has been elected (Article 31).
5. ☒ 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. ☐ 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. ☒ 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. ☒ 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)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☒ A copy of the International Search Report (PCT/ISA/210).

Items 13 to 23 below concern document(s) or information included:

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A power of attorney and/or change of address letter.
19. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13*ter*.2 and 37 CFR 1.821 - 1.825.
20. ☐ A second copy of the published International Application under 35 U.S.C. 154(d)(4).
21. ☐ A second copy of the English language translation of the International Application under 35 U.S.C. 154(d)(4).
22. ☐ Express Mail Label No.
23. ☒ Other items or information:

Notice of Claim for Priority
Cover Sheet of WO 03/1005856
Application Data Sheet

U.S. APPLICATION NO (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
10/518016	PCT/GB03/02557	TPP31753

24. The following fees are submitted:	CALCULATIONS PTO USE ONLY	
☒ a) Basic national fee $300.00		
☒ b) Examination fee $200.00		
☒ c) Search fee $500.00		
TOTAL OF ABOVE CALCULATIONS = $1000.00		
☐ Additional fee for specification and drawings filed in paper over 100 sheets (excluding sequence listing or computer program listing filed in an electronic medium). The fee is $250 for each additional 50 sheets of paper or fraction thereof.		
Total Sheets: - 100 = / Extra sheets: /50 = / Number of each additional 50 or fraction thereof (round up to a whole number) / RATE: x $250.00	$1,000.00	
Surcharge of $130.00 for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$0.00	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	51 - 20 =	31	x $50.00	$1,550.00	
Independent claims	3 - 3 =	0	x $200.00	$0.00	
Multiple Dependent Claims (check if applicable).			☐	$0.00	
TOTAL OF ABOVE CALCULATIONS =				$2,550.00	
☐ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.				$0.00	
SUBTOTAL =				$2,550.00	
Processing fee of $130.00 for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				$0.00	
TOTAL NATIONAL FEE =				$2,550.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) (check if applicable). ☐				$0.00	
TOTAL FEES ENCLOSED =				$2,550.00	
				Amount to be: refunded	$
				charged	$

a. ☒ A check in the amount of $2550.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of _____ to cover the above fees.

c. ☒ The Director is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 19-4375

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

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 International Application to pending status.

SEND ALL CORRESPONDENCE TO:

Thomas P. Pavelko
STEVENS, DAVIS, MILLER & MOSHER, LLP
1615 L Street N.W., Suite 850
Washington, D.C. 20036
Tel: 202-785-0100
Fax: 202-785-0200

SIGNATURE

Thomas P. Pavelko
NAME

31,689
REGISTRATION NUMBER

December 14, 2004
DATE

FORM PTO-1390 (Modified) (REV. 07-2004) U.S. PATENT AND TRADEMARK OFFICE; U.S. DEPARTMENT OF COMMERCE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A SUBMISSION UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	U.S. APPLICATION NO. (If known, see 37 CFR 1.5)
TPP31753	10/518016

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/GB03/02557	13 June 2003	14 June 2002

TITLE OF INVENTION
COMBINATION OF AZELASTINE AND STEROIDS

APPLICANT(S) FOR DO/EO/US
Amar LULLA
Geena MALHORTRA

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

1. ☒ This is a **FIRST** submission of items concerning a submission under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a submission under 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 (24) indicated below.
4. ☒ The US has been elected (Article 31).
5. ☒ 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. ☐ 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. ☒ 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. ☒ 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)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☒ A copy of the International Search Report (PCT/ISA/210).

Items 13 to 23 below concern document(s) or information included:

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A power of attorney and/or change of address letter.
19. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13*ter*.2 and 37 CFR 1.821 - 1.825.
20. ☐ A second copy of the published International Application under 35 U.S.C. 154(d)(4).
21. ☐ A second copy of the English language translation of the International Application under 35 U.S.C. 154(d)(4).
22. ☐ Express Mail Label No.
23. ☒ Other items or information:

Notice of Claim for Priority
Cover Sheet of WO 03/1005856
Application Data Sheet

U.S. APPLICATION NO (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
10/518016	PCT/GB03/02557	TPP31753

24. The following fees are submitted:		CALCULATIONS PTO USE ONLY
☒ a) Basic national fee	$300.00	
☒ b) Examination fee	$200.00	
☒ c) Search fee	$500.00	
TOTAL OF ABOVE CALCULATIONS =	$1000.00	

☐ Additional fee for specification and drawings filed in paper over 100 sheets (excluding sequence listing or computer program listing filed in an electronic medium). The fee is $250 for each additional 50 sheets of paper or fraction thereof.

Total Sheets	Extra sheets	Number of each additional 50 or fraction thereof (round up to a whole number)	RATE
- 100 =	/50 =		x $250.00

	$1,000.00	
Surcharge of $130.00 for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$0.00	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	51 - 20 =	31	x $50.00	$1,550.00	
Independent claims	3 - 3 =	0	x $200.00	$0.00	
Multiple Dependent Claims (check if applicable).			☐	$0.00	
TOTAL OF ABOVE CALCULATIONS =				$2,550.00	
☐ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.				$0.00	
SUBTOTAL =				$2,550.00	
Processing fee of $130.00 for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				$0.00	
TOTAL NATIONAL FEE =				$2,550.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) (check if applicable). ☐				$0.00	
TOTAL FEES ENCLOSED =				$2,550.00	
				Amount to be: refunded	$
				charged	$

a. ☒ A check in the amount of $2550.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of _____ to cover the above fees.

c. ☒ The Director is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 19-4375

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

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 International Application to pending status.

SEND ALL CORRESPONDENCE TO:

Thomas P. Pavelko
STEVENS, DAVIS, MILLER & MOSHER, LLP
1615 L Street N.W., Suite 850
Washington, D.C. 20036
Tel: 202-785-0100
Fax: 202-785-0200

SIGNATURE

Thomas P. Pavelko
NAME

31,689
REGISTRATION NUMBER

December 14, 2004
DATE

COMBINATION OF AZELASTINE AND STEROIDS

The present invention relates to pharmaceutical products and formulations. More particularly the present invention relates to pharmaceutical products and formulations useful for preventing or minimising allergic reactions. More particularly, but not exclusively, the present invention relates to pharmaceutical products and formulations for nasal and ocular use.

Such allergic reactions commonly comprise the allergy-related and vasomotor-related symptoms and the rhinovirus-related symptoms.

It is known to use antihistamines in nasal sprays and eye drops to treat allergy-related conditions. Thus, for example, it is known to use the antihistamine azelastine (usually as the hydrochloride salt) as a nasal spray against seasonal or perennial allergic rhinitis, or as eye drops against seasonal and perennial allergic conjunctivitis.

It is also known to treat these conditions using a corticosteroid, which will suppress nasal and ocular inflammatory conditions. Among the corticosteroids known for nasal use are, for example, beclomethasone, mometasone, fluticasone, budesonide and cyclosenide. Corticosteroids known for ocular anti-inflammatory use include betamethasone sodium, dexamethasone sodium and prednisolone acetate, for example.

It would be highly desirable, however, to provide a treatment that combines the effects of anti-histamine treatments and steroid treatments, in a pharmaceutically acceptable formulation, which is tolerated in situ, without significantly disrupting the potency of the constituent pharmaceuticals.

We have now found that, very surprisingly, azelastine (4-[(4-Chlorophenyl)methyl]-2-(hexahydro-1-methyl-1H-azepin-4-yl)-1(2H)-phthalazinone), or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, preferably in salt form and even more preferably in the form of the hydrochloride salt, can advantageously be combined with a steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, to provide a stable, very effective combination product or formulation preferably for nasal or ocular treatment. The combination can provide, in a single administration or dosing regime, the antihistaminic properties of azelastine and the anti-

inflammatory (and / or other) properties of the steroid, without any significant interference between the two, or adverse reaction in situ.

In one aspect the invention provides a pharmaceutical formulation comprising azelastine or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, and a steroid, preferably a corticosteroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, the formulation preferably being in a form suitable for administration nasally or ocularly.

The term "physiologically functional derivative" as used herein denotes a chemical derivative of any of the specific therapeutic agents described herein having the same or similar physiological function as the free base therapeutic agent and, for example, being convertible in the body thereto. According to the present invention, examples of physiologically functional derivatives include esters.

The preferred forms of formulations of the invention are nasal drops, eye drops, nasal sprays, nasal inhalation solutions or aerosols or insufflation powders.

Preferred embodiments of the invention can comprise stable aqueous solutions of azelastine or one or more of its salts, in combination with steroids which may be beclomethasone, mometasone, fluticasone, budesonide or cyclosenide, which can be used in the form of inhalation solution, pressurized aerosol, eye drops or nasal drops, and in a particular preferred embodiment, in the form of a spray (preferably a nasal spray). The spray can, for example, be formed by the use of a conventional spray-squeeze bottle or a pump vaporizer. In addition, it is also possible to use compressed gas aerosols. In a preferred embodiment, 0.03 to 3 mg of azelastine base and 0.05 to 0.15 mg of the steroid should be released per individual actuation.

The formulations preferably contain a preservative and/or stabilizer. These include, for example: ethylene diamine tetra-acetic acid (edetic acid) and its alkali salts (for example dialkali salts such as disodium salt, calcium salt, calcium-sodium salt), lower alkyl p-hydroxybenzoates, chlorhexidine (for example in the form of the acetate or gluconate) and phenyl mercury borate. Other suitable preservatives are: pharmaceutically useful quaternary ammonium compounds, for example cetylpyridinium chloride, tetradecyltrimethyl ammonium bromide, generally known as "cetrimide", benzyldimethyl-[2-[2-[p-(1,1,3,3-tetramethyl-butyl)phenoxy]ethoxy]-ammonium chloride, generally known as "benzethonium chloride" and myristyl picolinium chloride. Each of these compounds may be used in a

concentration of 0.002 to 0.05%, for example 0.02% (weight/volume in liquid formulations, otherwise weight/weight). Preferred preservatives among the quaternary ammonium compounds are, however, alkylbenzyl dimethyl ammonium chloride and mixtures thereof, for example the compounds generally known as "benzalkonium chloride".

The total amount of preservatives in the formulations (solutions, ointments, etc.) is preferably from 0.001 to 0.10g, preferably 0.01g per 100ml of solution/suspension or 100g of formulation.

In the case of preservatives, the following amounts of individual substances can, for example, be used: thimero sal 0.002-0.02%; benzalkonium chloride 0.002 to 0.02% (in combination with thimero sal the amount of thimero sal is, for example =0.002 to 0.005%;); chlorhexidine acetate or gluconate 0.01 to 0.02%; phenyl mercuric/nitrate, borate, acetate 0.002-0.004%; p-hydroxybenzoic acid ester (for example, a mixture of the methyl ester and propyl ester in the ratio 7:3): preferably 0.05-0.15, more preferably 0.1%.

The preservative used is preferably a combination of edetic acid (for example, as the disodium salt) and benzalkonium chloride. In this combination, the edetic acid is preferably used in a concentration of 0.05 to 0.1%, benzalkonium chloride preferably being used in a concentration of 0.005 to 0.05%, more preferably 0.01%.

In the case of solutions/suspensions reference is always made to percent by weight/volume, in the case of solid or semi-solid formulations to percent by weight/weight of the formulation.

Further auxiliary substances which may, for example, be used for the formulations of the invention are: polyvinyl pyrrolidone, sorbitan fatty acid esters such as sorbitan trioleate, polyethoxylated sorbitan fatty acid esters (for example polyethoxylated sorbitan trioleate), sorbimacrogol oleate, synthetic amphotensides (tritons), ethylene oxide ethers of octylphenolformaldehyde condensation products, phosphatides such as lecithin, polyethoxylated fats, polyethoxylated oleotriglycerides and polyethoxylated fatty alcohols. In this context, polyethoxylated means that the relevant substances contain polyoxyethylene chains, the degree of polymerisation of which is generally between 2 to 40, in particular between 10 to 20. These substances are preferably used to improve the solubility of the azelastine component.

It is optionally possible to use additional isotonization agents. Isotonization agents which may, for example, be used are: saccharose, glucose, glycerine, sorbitol, 1,2-propylene

glycol and NaCl.

The isotonization agents adjust the osmotic pressure of the formulations to the same osmotic pressure as nasal secretion. For this purpose these substances are in each case to be used in such amount that, for example, in the case of a solution, a reduction in the freezing point of 0.50 to 0.56 degree C is attained in comparison to pure water.

In Example 1, it is possible to use instead of NaCl per 100 ml of solution, for example: Glucose $1H_2O$ 3.81g; saccharose 6.35g; glycerine 2.2g; 1,2-propylene glycol 1.617g; sorbitol 3.84g (in the case of mixtures of these substances correspondingly less may optionally be used).

Moreover, it is possible to add thickening agents to solutions according to the present invention to prevent the solution from flowing out of the nose too quickly and to give the solution a viscosity of about 1.5 to 3, preferably 2 mPa.

Such thickening agents may, for example, be: cellulose derivatives (for example cellulose ether) in which the cellulose-hydroxy groups are partially etherified with lower unsaturated aliphatic alcohols and/or lower unsaturated aliphatic oxyalcohols (for example methyl cellulose, carboxymethyl cellulose, hydroxypropylmethylcellulose), gelatin, polyvinylpyrrolidone, tragacanth, ethoxose (water soluble binding and thickening agents on the basis of ethyl cellulose), alginic acid, polyvinyl alcohol, polyacrylic acid, pectin and equivalent agents. Should these substances contain acid groups, the corresponding physiologically acceptable salts may also be used.

In the event of the use of hydroxypropyl cellulose, 0.1% by weight of the formulation, for example, is used for this purpose.

In the event of the use of Avicel RC 591 or CLll, 0.65-3.0% by weight of the formulation, for example, is used for the purpose.

It is also possible to add to the formulations buffer substances such as citric acid/sodium hydrogensulphate borate buffer, phosphates (sodium hydrogenorthophosphate, disodium hydrogenphosphate), trometamol or equivalent conventional buffers in order, for example, to adjust the formulations to a pH value of 3 to 7, preferably 4.5 to 6.5.

The amount of citric acid is, for example, 0.01 to 0.14g, preferably 0.04 to 0.05g, the amount of disodium hydrogenphosphate 0.1 to 0.5g, preferably 0.2 to 0.3g per 100 ml of solution. The weights given relate in each case to the anhydrous substances.

In the case of solutions and suspensions, the maximum total concentration of active agent and buffer is preferably less than 5%, in particular less than 2% (weight/volume).

For the nasal application, a solution or suspension can preferably be used which is applied as an aerosol, i.e. in the form of a fine dispersion in air or in another conventional carrier gas, for example by means of a conventional pump vaporizer.

Application as a dosage aerosol is, however, also possible. Dosage aerosols are defined as being pressure packings which contain the azelastine or its salts in combination with steroid, in the form of a solution or suspension in a so-called propellant. The propellant may be a pressurized liquid chlorinated, fluorinated hydrocarbon or mixtures of various chlorinated, fluorinated hydrocarbons as well as propane, butane, isobutene or mixtures of these among themselves or with chlorinated, fluorinated hydrocarbons which are gaseous at atmospheric pressure and room temperature. Hydrofluorocarbons (HFCs), such as HFC 134a, and HFC 227a can also be used, and are preferred for environmental reasons. The pressure packing has a dosage or metering valve which, on actuation, releases a defined amount of the solution or suspension of the medicament. The subsequent very sudden vaporization of the propellant tears the solution or suspension of azelastine into the finest droplets or minute particles which can be sprayed in the nose or which are available for inspiration into the nose. Certain plastic applicators may be used to actuate the valve and to convey the sprayed suspension into the nose.

In the case of application as an aerosol, it is also possible to use a conventional adapter.

Particularly preferred embodiments of the present invention are hereinafter described and it will of course be appreciated that any of the previous description of suitable ingredients and formulation characteristics can also be applicable to the following products and formulations as provided by the present invention.

It will be appreciated, therefore, that the present invention further provides a pharmaceutical product comprising (i) azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, provided in an aerosol formulation preferably together with a propellant typically suitable for MDI delivery, and (ii) at least one steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, provided in an aerosol formulation preferably together with a propellant typically suitable for MDI delivery, as a combined preparation for simultaneous, separate or sequential

use in the treatment of conditions for which administration of one or more anti-histamine and / or one or more steroid is indicated.

The present invention also provides an aerosol formulation preferably suitable for MDI delivery comprising (i) azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, and (ii) at least one steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, together with a propellant.

It will also be appreciated from the above, that the respective therapeutic agents of the combined preparation can be administered simultaneously, either in the same or different pharmaceutical formulations, or separately or sequentially. If there is separate or sequential administration, it will also be appreciated that the subsequently administered therapeutic agents should be administered to a patient within a time scale so as to achieve, or more particularly optimise, the above referred to advantageous synergistic therapeutic effect of a combined preparation as present in a pharmaceutical product according to the present invention.

Suitable propellants for use in pharmaceutical products of formulations as provided by the present invention include 1,1,1,2-tetrafluoroethane (HFA 134a) or 1,1,1,2,3,3,3,-heptafluoropropane (HFA 227), or a combination of both, or mono-fluoro trichloromethane and dichloro difluoromethane, in particular 1,1,1,2-tetrafluoroethane (HFA 134a) or 1,1,1,2,3,3,3-heptafluoropropane (HFA 227), with HFA 134a being preferred.

A pharmaceutical aerosol formulation according to the present invention preferably further comprises a polar cosolvent such as C_{2-6} aliphatic alcohols and polyols, for example ethanol, isopropanol and propylene glycol, with ethanol often being preferred. Preferably, the concentration of the cosolvent is in the range of about 2 to 10% by weight, typically up to about 5%, of the total formulation.

A pharmaceutical aerosol formulation according to the present invention may further comprise one or more surfactants. Such surfactants can be included to stabilise the formulations and for lubrication of a valve system. Some of the most commonly used surfactants in aerosol formulations are oils derived from natural sources, such as corn oil, olive oil, cottonseed oil and sunflower seed oil, and also phospholipids. Suitable surfactants can include lecithin, oleic acid or sorbitan oleate.

A further preferred embodiment of the present invention can be where a formulation

or product is provided in the form of insufflatable powder, where preferably the maximum particle size of the substance suitably does not exceed 10μm. Azelastine or its salts and the steroid may be mixed with inert carrier substances or drawn up onto inert carrier substances. Carrier substances which may, for example, be used are: sugars such as glucose, saccharose, lactose and fructose. Also starches or starch derivatives, oligosaccharides such as dextrins, cyclodextrins and their derivatives, polyvinylpyrrolidone, alginic acid, tylose, silicic acid, cellulose, cellulose derivatives (for example cellulose ether), sugar alcohols such as mannitol or sorbitol, calcium carbonate, calcium phosphate, etc.

In one embodiment, the therapeutic agents employed have a particle size of less than about 10 μm, preferably less than 5 μm.

The use of insufflation powders can represent a preferred embodiment of the present invention and there is provided by the present invention a pharmaceutical product comprising (i) azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, provided as an insufflation powder, and (ii) at least one steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, provided as an insufflation powder, as a combined preparation for simultaneous, separate or sequential use in the treatment of conditions for which administration of one or more anti-histamine and / or one or more steroid is indicated.

It will be appreciated from the above, that the respective therapeutic agents of the combined preparation can be administered simultaneously, either in the same or different insufflation powder formulations, or separately or sequentially. If there is separate or sequential administration as discussed above, it will also be appreciated that the subsequently administered therapeutic agents should be administered to a patient within a time scale so as to achieve, or more particularly optimise, the above referred to advantageous synergistic therapeutic effect of a combined preparation as present in a pharmaceutical product according to the present invention.

The present invention also provides an insufflation powder formulation comprising (i) azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, and (ii) at least one steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, together with a pharmaceutically acceptable carrier or excipient therefor.

Dry insufflation powder formulations as provided by the present invention can be

beneficial where it is required that therapeutic agents as employed according to the present invention are retained in the nasal cavity, and systemic side effects can be minimised or eliminated. Furthermore, insufflation powder formulations as employed in the present invention can be beneficial whereby retention of azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, at the nasal mucosa is improved, and the bitter aftertaste associated with liquid antihistamine formulations significantly reduced, whilst also exhibiting the synergistic therapeutic effect associated with the azelastine / steroid combinations provided by the present invention. By providing a dry insufflation powder formulation of azelastine, together with a steroid, having an average particle size of less than about 10 μm, the therapeutic agents can be restricted primarily to the desired target organ, the nasal mucosa.

A dry powder insufflation formulation according to the present invention can be administered by the use of an insufflator, which can produce a finely divided cloud of the dry powder. The insufflator preferably is provided with means to ensure administration of a substantially pre-determined amount of a formulation or product as provided by the present invention. The powder may be used directly with an insufflator which is provided with a bottle or container for the powder, or the powder may be filled into a capsule or cartridge, such as a gelatin capsule, or other single dose device adapted for administration. The insufflator preferably has means to open the capsule or other dose device.

Preferred combinations of therapeutic agents employed in pharmaceutical products and formulations according to the present invention (in particular nasal sprays or drops, aerosol or insufflation products and formulations as described above) comprise any one of the following combinations.

The present invention further provides, therefore, a pharmaceutical product comprising (i) azelastine, or a pharmaceutically acceptable salt thereof, and (ii) at least one steroid selected from the group consisting of beclomethasone, fluticasone, mometasone and pharmaceutically acceptable esters thereof, as a combined preparation for simultaneous, separate or sequential use in the treatment of conditions for which administration of one or more anti-histamine and / or one or more steroid is indicated. Suitably the esters can be selected from beclomethasone dipropionate, fluticasone propionate, fluticasone valerate, mometasone furoate and mometasone furoate monohydrate.

The present invention also provides a pharmaceutical formulation comprising (i) azelastine, or a pharmaceutically acceptable salt thereof, and (ii) at least one steroid selected from the group consisting of beclomethasone, fluticasone, mometasone and pharmaceutically acceptable esters thereof, together with a pharmaceutically acceptable carrier or excipient therefor. Suitably the esters can be selected from beclomethasone dipropionate, fluticasone propionate, fluticasone valerate, mometasone furoate and mometasone furoate monohydrate.

In the case of a nasal spray, a particularly preferred formulation as provided by the present invention is a nasal spray comprising azelastine, or a pharmaceutically acceptable salt thereof (preferably azelastine hydrochloride), together with mometasone either as the free base or in ester form, preferably as mometasone furoate.

Specific combinations of therapeutic agents employed in pharmaceutical products and formulations according to the present invention comprise any one of the following combinations:

azelastine hydrochloride and beclomethasone dipropionate;

azelastine hydrochloride and fluticasone propionate;

azelastine hydrochloride and fluticasone valerate;

azelastine hydrochloride and mometasone furoate; and

azelastine hydrochloride and mometasone furoate monohydrate.

There is also provided by the present invention a method for the prophylaxis or treatment in a mammal, such as a human, of conditions for which administration of one or more anti-histamine and / or one or more steroid is indicated, which method comprises administration of a therapeutically effective amount of a pharmaceutical product substantially as hereinbefore described, as a combined preparation for simultaneous, separate or sequential use in the treatment of such conditions.

The present invention also provides a method for the prophylaxis or treatment in a mammal, such as a human, of conditions for which administration of one or more anti-histamine and / or one or more steroid is indicated, which method comprises administration of a therapeutically effective amount of a pharmaceutical formulation substantially as hereinbefore described.

There is also provided by the present invention for use in the manufacture of a medicament for the prophylaxis or treatment in a mammal, such as a human, of conditions for which administration of one or more anti-histamine and / or one or more steroid is indicated,

a pharmaceutical product, as a combined preparation for simultaneous, separate or sequential use in the treatment of such conditions.

There is further provided by the present invention, therefore, a process of preparing a pharmaceutical product substantially as hereinbefore described, which process comprises providing as a combined preparation for simultaneous, separate or sequential use in the treatment of conditions for which administration of one or more anti-histamine and / or one or more steroid is indicated: (i) azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, and (ii) at least one steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.

The present invention also provides a process of preparing a pharmaceutical formulation substantially as hereinbefore described, which process comprises admixing a pharmaceutically acceptable carrier or excipient with: (i) azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, and (ii) at least one steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof. Preferably pharmaceutical formulations according to the present invention can comprise insufflation powder formulations, nasal sprays, nasal inhalation solutions or aerosols substantially as hereinbefore described.

The present invention is now illustrated by the following Examples, which do not limit the scope of the invention in any way. In Examples where only the ingredients of formulations according to the present invention are listed, these formulations are prepared by techniques well known in the art.

Example 1

Nasal spray or nasal drops with 0.1% azelastine hydrochloride as active ingredient and steroid 0.1%

Sr. No	Ingredients	Quantity %w/v
1.	Azelastine hydrochloride	0.1%
2.	Steroid	0.1%
3.	Disodium edetate	0.005%

4.	Sodium chloride	0.9%
5.	Benzalkonium chloride	0.001%
6.	Avicel RC 591	1.2%
7.	Citric acid monohydrate	0.2%
8.	Disodium hydrogen phosphate dodecahydrate	0.1%
9.	Purified water	

Example 2

Dosage aerosol giving off 0.5 mg of azelastine hydrochloride and 50 micrograms of beclomethasone dipropionate freon solvate per stroke.

About 8.0 kg of a mixture of 70 parts by weight of difluorodichloromethane and 30 parts by weight of 1,2dichlorotetrafluoroethane are cooled to about -55 degree C in an appropriate cooling vessel. A mixture of 0.086 kg of pre-cooled sorbitantrioleate and 0.8600 kg of pre-cooled trichlorofluoromethane are dissolved with stirring into the mixture at -55 degrees C, 0.0688 kg of micronized azelastine hydrochloride, 0.00688 kg of beclomethasone dipropionate freon solvate and 0.0688 kg of micronized lactose are then incorporated in portions into the solution thereby obtained with intensive stirring. The total weight of the suspension thereby obtained is made up to 9.547 kg through addition of more of the mixture of 70 parts by weight of difluorodichloromethane and 30 parts by weight of 1,2-dichlorotetrafluoroethane cooled to about -55 degree C.

Following closure of the cooling vessel the suspension is again cooled to about -55 degrees C under intensive stirring. It is then ready to be filled.

Example 3

Nasal spray or nasal drops with Azelastine and steroid*

Sr. No.	Ingredients	Quantity (% w/w)
	Azelastine Hydrochloride	0.10

	Fluticasone propionate	0.0357
	Glycerin	2.60
	Avicel RC 591	1.35
	Polysorbate 80	0.025
	Benzalkonium chloride	0.01
	Phenyl ethyl alcohol	0.25
	Purified water	q. s.

*Each spray delivers Azelastine Hydrochloride (140 mcg) and Fluticasone propionate (50 mcg).

Example 4

Nasal spray or nasal drops with Azelastine and steroid*

Sr. No.	Ingredients	Quantity (% w/w)
	Azelastine Hydrochloride	0.10
	Fluticasone valerate	0.0357
	Glycerin	2.60
	Avicel RC 591	1.20
	Polysorbate 80	0.030
	Benzalkonium chloride	0.01
	Phenyl ethyl alcohol	0.25
	Purified water	q. s.

*Each spray delivers Azelastine Hydrochloride (140 mcg) and Fluticasone valerate (50 mcg).

Example 5

Nasal spray or nasal drops with Azelastine and steroid*

Sr. No.	Ingredients	Quantity (% w/w)
	Azelastine Hydrochloride	0.10
	Fluticasone propionate	0.0714
	Glycerin	2.60
	Avicel RC 581	1.35
	Polysorbate 80	0.025
	Benzalkonium chloride	0.01
	Phenyl ethyl alcohol	0.25
	Purified water	q. s.

*Each spray delivers Azelastine Hydrochloride (140 mcg) and Fluticasone propionate (50 mcg).

Example 6

Nasal spray or nasal drops with Azelastine and steroid

Sr. No.	Ingredients	Quantity (% w/w)
	Azelastine Hydrochloride	0.10
	Mometasone Furoate	0.05173
	Glycerin	2.30
	Disodium edetate	0.005
	Polysorbate 80	0.0125
	Avicel RC 581	1.35
	Benzalkonium chloride	0.01
	Citric acid monohydrate	0.20
	Disodium hydrogen phosphate	0.10

	dodecahydrate	
	Purified water	q. s.

Example 7

Nasal spray or nasal drops with Azelastine and steroid*

Sr. No.	Ingredients	Quantity (% w/w)
	Azelastine Hydrochloride	0.10
	Mometasone Furoate monohydrate	0.05173
	Glycerin	2.60
	Avicel CL 611	2.295
	Polysorbate 80	0.0125
	Benzalkonium chloride	0.01
	Phenyl ethyl alcohol	0.25
	Purified water	q. s.

*Each spray delivers Azelastine Hydrochloride (140 mcg) and Mometasone furoate (50 mcg).

Example 8

Nasal MDI with Azelastine and steroid

Sr. No.	Ingredients	Quantity in mcg
	Azelastine Hydrochloride	140
	Mometasone Furoate monohydrate	50
	HFA 134a	q.s.
	Lecithin	0.1%
	Alcohol	(up to 5%)

Example 9

Nasal MDI with Azelastine and steroid

Sr. No.	Ingredients	Quantity in mcg
	Azelastine Hydrochloride	140
	Fluticasone propionate	50
	HFA 134a	q.s.
	Sorbitan trioleate	0.1%
	Alcohol	(up to 5%)

Example 10

Nasal MDI with Azelastine and steroid

Sr. No.	Ingredients	Quantity in mcg
	Azelastine Hydrochloride	140
	Fluticasone propionate	100
	HFA 134a	q.s.
	Oleic acid	0.1%

Example 11

Nasal MDI with Azelastine and steroid

Sr. No.	Ingredients	Quantity in mcg
	Azelastine Hydrochloride	140
	Fluticasone Valerate	50
	HFA 134a	q.s.
	Alcohol	(up to 5%)

Insufflatable powders containing Azelastine and Steroid:

Example 12

Sr. No.	Ingredients	Quantity (% w/w)
	Azelastine Hydrochloride (Micronized)	140 mcg
	Fluticasone propionate	50 mcg
	Lactose	q.s. (up to 25 mcg)

Example 13

Sr. No.	Ingredients	Quantity (% w/w)
	Azelastine Hydrochloride (Micronized)	140 mcg
	Fluticasone propionate	100 mcg
	Mannitol	q.s. (up to 30 mcg)

Example 14

Sr. No.	Ingredients	Quantity (% w/w)
	Azelastine Hydrochloride (Micronized)	140 mcg
	Fluticasone propionate	250 mcg
	Lactose	q.s. (up to 30 mcg)

CLAIMS:

1 A pharmaceutical formulation which comprises azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, and a steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, preferably the formulation being in a form suitable for nasal or ocular administration.

2 A pharmaceutical formulation according to claim 1, wherein said azelastine is present as azelastine hydrochloride.

3 A formulation according to claim 1 or 2, wherein the steroid is beclomethasone or a pharmaceutically acceptable ester thereof, mometasone or a pharmaceutically acceptable ester thereof, fluticasone or a pharmaceutically acceptable ester thereof, budesonide or cyclosenide, in any chiral form or mixture.

4 A formulation according to claim 3, wherein the steroid is beclomethasone propionate, mometasone furoate, mometasone furoate monohydrate, fluticasone propionate or fluticasone valerate.

5 A formulation according to any of claims 1 to 4, which contains the steroid in an amount from about 50 micrograms/ml to about 5 mg/ml of the formulation.

6 A formulation according to any of claims 1 to 5, wherein the formulation has a particle size of less than about 10 μm, preferably less than 5 μm.

7 A formulation according to any of claims 1 to 6, which is a suspension containing 0.0005 to 2% (weight/weight of the formulation) of azelastine or a pharmaceutically acceptable salt of azelastine, and from 0.5 to 1.5% (weight/weight of the formulation) of said steroid.

8 A formulation according to claim 7, which contains from 0.001 to 1% (weight/weight of the formulation) azelastine, or salt thereof, and from 0.5% to 1.5% (weight/weight of the

formulation) steroid.

9 A formulation according to any of claims 1 to 8, which also contains a surfactant.

10 A formulation according to claim 9, wherein the surfactant comprises a polysorbate or poloxamer surfactant.

11 A formulation according to claim 9 or 10, which contains from about 50 micrograms to about 1 milligram of surfactant per ml of the formulation.

12 A formulation according to any of claims 1 to 11, which also contains an isotonic agent.

13 A formulation according to claim 12, wherein the isotonic agent comprises sodium chloride, saccharose, glucose, glycerine, sorbitol or 1,2-propylene glycol.

14 A formulation according to any of claims 1 to 13, which also contains at least one of a buffer, a preservative and a suspending or thickening agent.

15 A formulation according to claim 14, wherein said preservative is selected from edetic acid and its alkali salts, lower alkyl p-hydroxybenzoates, chlorhexidine, phenyl mercury borate, or benzoic acid or a salt, a quaternary ammonium compound, or sorbic acid or a salt thereof.

16 A formulation according to claim 14 or 15, wherein the suspending agent or thickening agent is selected from cellulose derivatives, gelatin, polyvinylpyrrolidone, tragacanth, ethoxose (water soluble binding and thickening agents on the basis of ethyl cellulose), alginic acid, polyvinyl alcohol, polyacrylic acid, or pectin.

17 A formulation according to any of claims 14, 15 or 16, wherein the buffer comprises a citric acid-citrate buffer.

18 A formulation according to any of claims 14, 15, 16 or 17, wherein the buffer maintains the pH of the aqueous phase at from 3 to 7, preferably 4.5 to about 6.5.

19 A formulation according to any of claims 1 to 18, which is an aqueous suspension or solution.

20 A formulation according to claim 19, which is in the form of an aerosol, an ointment, eye drops, nasal drops, a nasal spray or an inhalation solution.

21 A formulation according to claim 20, which is in the form of nasal drops or nasal spray.

22 A formulation according to claim 20, which is in the form of an aerosol.

23 A pressure packing having a dosage or metering valve, which contains a formulation according to claim 22.

24 A MDI which includes a pressure packing according to claim 23.

25 A formulation according to any of claims 1 to 19, which is in the form of an insufflation powder.

26 A pharmaceutical product comprising (i) azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, provided in an aerosol formulation preferably together with a propellant typically suitable for MDI delivery, and (ii) at least one steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, provided in an aerosol formulation preferably together with a propellant typically suitable for MDI delivery, as a combined preparation for simultaneous, separate or sequential use in the treatment of conditions for which administration of one or more anti-histamine and / or one or more steroid is indicated.

27 An aerosol formulation preferably suitable for MDI delivery comprising (i) azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, and (ii) at least one steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, together with a propellant.

28 A pharmaceutical product comprising (i) azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, provided as an insufflation powder, and (ii) at least one steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, provided as an insufflation powder, as a combined preparation for simultaneous, separate or sequential use in the treatment of conditions for which administration of one or more anti-histamine and / or one or more steroid is indicated.

29 An insufflation powder formulation comprising (i) azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, and (ii) at least one steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, together with a pharmaceutically acceptable carrier or excipient therefor.

30 A pharmaceutical product comprising (i) azelastine, or a pharmaceutically acceptable salt thereof, and (ii) at least one steroid selected from the group consisting of beclomethasone, fluticasone, mometasone and pharmaceutically acceptable esters thereof, as a combined preparation for simultaneous, separate or sequential use in the treatment of conditions for which administration of one or more anti-histamine and / or one or more steroid is indicated.

31 A pharmaceutical formulation comprising (i) azelastine, or a pharmaceutically acceptable salt thereof, and (ii) at least one steroid selected from the group consisting of beclomethasone, fluticasone, mometasone and pharmaceutically acceptable esters thereof, together with a pharmaceutically acceptable carrier or excipient therefor.

32 A nasal spray comprising azelastine, or a pharmaceutically acceptable salt thereof, together with mometasone either as mometasone free base or as mometasone furoate, and a pharmaceutically acceptable carrier or excipient therefor.

33 A pharmaceutical product comprising azelastine hydrochloride and beclomethasone dipropionate, as a combined preparation for simultaneous, separate or sequential use in the treatment of conditions for which administration of one or more anti-histamine and / or one or more steroid is indicated.

34 A pharmaceutical formulation comprising azelastine hydrochloride and beclomethasone dipropionate, together with a pharmaceutically acceptable carrier or excipient therefor.

35 A pharmaceutical product comprising azelastine hydrochloride and fluticasone propionate, as a combined preparation for simultaneous, separate or sequential use in the treatment of conditions for which administration of one or more anti-histamine and / or one or more steroid is indicated.

36 A pharmaceutical formulation comprising azelastine hydrochloride and fluticasone propionate, together with a pharmaceutically acceptable carrier or excipient therefor.

37 A pharmaceutical product comprising azelastine hydrochloride and fluticasone valerate, as a combined preparation for simultaneous, separate or sequential use in the treatment of conditions for which administration of one or more anti-histamine and / or one or more steroid is indicated.

38 A pharmaceutical formulation comprising azelastine hydrochloride and fluticasone valerate, together with a pharmaceutically acceptable carrier or excipient therefor.

39 A pharmaceutical product comprising azelastine hydrochloride and mometasone furoate, as a combined preparation for simultaneous, separate or sequential use in the

treatment of conditions for which administration of one or more anti-histamine and / or one or more steroid is indicated.

40 A pharmaceutical formulation comprising azelastine hydrochloride and mometasone furoate, together with a pharmaceutically acceptable carrier or excipient therefor.

41 A pharmaceutical product comprising azelastine hydrochloride and mometasone furoate monohydrate, as a combined preparation for simultaneous, separate or sequential use in the treatment of conditions for which administration of one or more anti-histamine and / or one or more steroid is indicated.

42 A pharmaceutical formulation comprising azelastine hydrochloride and mometasone furoate monohydrate, together with a pharmaceutically acceptable carrier or excipient therefor.

43 A pharmaceutical formulation substantially as herein described in any of the Examples.

44 A process of preparing a pharmaceutical product according to any of claims 26, 28, 30, 33, 35, 37, 39 or 41, which process comprises providing (i) azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, and (ii) at least one steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, as a combined preparation for simultaneous, separate or sequential use in the treatment of conditions for which administration of one or more anti-histamine and / or one or more steroid is indicated.

45 A process of preparing a pharmaceutical formulation according to any of claims 1 to 22, 27, 29, 31, 32, 34, 36, 38, 40, 42 or 43, which process comprises admixing a pharmaceutically acceptable carrier or excipient with azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, and at least one steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.

46 A method for the prophylaxis or treatment in a mammal, such as a human, of conditions for which administration of one or more anti-histamine and / or one or more steroid is indicated, which method comprises administration of a therapeutically effective amount of a pharmaceutical product according to any of claims 26, 28, 30, 33, 35, 37, 39 or 41, as a combined preparation for simultaneous, separate or sequential use in the treatment of such conditions.

47 A method for the prophylaxis or treatment in a mammal, such as a human, of conditions for which administration of one or more anti-histamine and / or one or more steroid is indicated, which method comprises administration of a therapeutically effective amount of a pharmaceutical formulation according to any of claims 1 to 22, 27, 29, 31, 32, 34, 36, 38, 40, 42 or 43.

48 For use in the manufacture of a medicament for the prophylaxis or treatment in a mammal, such as a human, of conditions for which administration of one or more anti-histamine and / or one or more steroid is indicated, a pharmaceutical product according to any of claims 26, 28, 30, 33, 35, 37, 39 or 41, as a combined preparation for simultaneous, separate or sequential use in the treatment of such conditions.

49 A method of treating irritation or disorders of the nose or eye which comprises applying either directly to nasal tissues or to the conjunctival sac of the eyes, as appropriate, a pharmaceutical product according to any of claims 26, 28, 30, 33, 35, 37, 39 or 41, or a pharmaceutical formulation according to any of claims 1 to 22, 27, 29, 31, 32, 34, 36, 38, 40, 42 or 43.

50 A method of treating airway disorders, comprising administering by nebulization to surfaces of the airway a treatment-effective amount of a product or formulation as defined in the preceding claims.

MULTIPLE DEPENDENT CLAIM FEE CALCULATION SHEET

(FOR USE WITH FORM PTO-875)

SERIAL NO. 10/518016

FILING DATE

APPLICANT(S)

CLAIMS

	AS FILED		AFTER 1st AMENDMENT		AFTER 2nd AMENDMENT	
	IND.	DEP.	IND.	DEP.	IND.	DEP.
1			1			
2				1		
3				1		
4				1		
5				1		
6				1		
7				1		
8				1		
9				1		
10				1		
11				1		
12				1		
13				1		
14				1		
15				1		
16				1		
17				1		
18				1		
19				1		
20				1		
21				1		
22				1		
23				1		
24				1		
25				1		
26				1		
27				1		
28			1			
29			1			
30				1		
31				1		
32				1		
33				1		
34				1		
35				1		
36				1		
37				1		
38				1		
39				1		
40				1		
41				1		
42				1		
43						
44				1		
45				1		
46				1		
47				1		
48				1		
49				1		
50				1		
TOTAL IND.		↓	3	↓		↓
TOTAL DEP.		←	46	←		←
TOTAL CLAIMS			49			

	AS FILED		AFTER 1st AMENDMENT		AFTER 2nd AMENDMENT	
	IND.	DEP.	IND.	DEP.	IND.	DEP.
51				1		
52				1		
53						
54						
55						
56						
57						
58						
59						
60						
61						
62						
63						
64						
65						
66						
67						
68						
69						
70						
71						
72						
73						
74						
75						
76						
77						
78						
79						
80						
81						
82						
83						
84						
85						
86						
87						
88						
89						
90						
91						
92						
93						
94						
95						
96						
97						
98						
99						
100						
TOTAL IND.		↓	0	↓		↓
TOTAL DEP.		←	2	←		←
TOTAL CLAIMS			2			

PATENT APPLICATION FEE DETERMINATION RECORD

Effective December 8, 2004

Application or Docket Number: 10/518016

CLAIMS AS FILED - PART I

	(Column 1)	(Column 2)	SMALL ENTITY TYPE ☐		OR	OTHER THAN SMALL ENTITY	
			RATE	FEE		RATE	FEE
U.S. NATIONAL STAGE FEES							
BASIC FEE	SMALL ENT. = $ 150	LARGE ENT. = $ 300	BASIC FEE		OR	BASIC FEE	300
EXAMINATION FEE	Satisfies PCT Article 33(1)-(4) = $ 50 / $ 100	All other situations = $ 100 / $ 200	EXAM. FEE			EXAM. FEE	200
SEARCH FEE	U.S. is ISA = $ 50 / $ 100 ALL other countries = $ 200 / $ 400	All other situations = $ 250 / $ 500	SEARCH FEE			SEARCH FEE	400
FEE FOR EXTRA SPEC. PGS.	minus 100 =	/ 50 =	X $ 125 =			X $ 250 =	
TOTAL CHARGEABLE CLAIMS	51 minus 20 =	* 31	X $ 25 =		OR	X $ 50 =	1550
INDEPENDENT CLAIMS	3 minus 3 =	*	X $ 100 =		OR	X $ 200 =	
MULTIPLE DEPENDENT CLAIM PRESENT	☐		+ $ 180 =		OR	+ $ 360 =	
* If the difference in column 1 is less than zero, enter "0" in column 2			TOTAL		OR	TOTAL	2450

CLAIMS AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
AMENDMENT A	Total	*	Minus	**	=
	Independent	*	Minus	***	=
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM ☐				

SMALL ENTITY RATE	SMALL ENTITY ADDITIONAL FEE	OR	OTHER THAN SMALL ENTITY RATE	OTHER THAN SMALL ENTITY ADDITIONAL FEE
X $ 25 =		OR	X $ 50 =	
X $ 100 =		OR	X $ 200 =	
+ $ 180 =		OR	+ $ 360 =	
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 ☐				

SMALL ENTITY RATE	SMALL ENTITY ADDITIONAL FEE	OR	OTHER THAN SMALL ENTITY RATE	OTHER THAN SMALL ENTITY ADDITIONAL FEE
X $ 25 =		OR	X $ 50 =	
X $ 100 =		OR	X $ 200 =	
+ $ 180 =		OR	+ $ 360 =	
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.

PATENT APPLICATION SERIAL NO. _____

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE
FEE RECORD SHEET

12/22/2004 GFREY1 00000063 10518016

01 FC:1631 300.00 OP
~~02 FC:1632 500.00 OP~~
03 FC:1633 200.00 OP
04 FC:1615 1550.00 OP

Adjustment date: 08/12/2005 ATRAN1
12/22/2004 GFREY1 00000063 10518016
02 FC:1632 -500.00 OP

08/12/2005 ATRAN1 00000001 10518016

01 FC:1642 400.00 OP

Repln. Ref: 08/12/2005 ATRAN1 0014431400
DA#:194375 Name/Number:10518016
FC: 9204 $100.00 CR

PTO-1556
(5/87)

*U.S. Government Printing Office: 2002 — 489-267/69033

Rec'd PCT/PTO 06 JUL 2005

PTO-1390 (Rev. 02-2005)
Approved for use through 3/31/2007. OMB 0651-0021
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

U.S. APPLICATION NO (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
10/518,016	PCT/GB02/02557	TPP 31753

The following fees are submitted:		CALCULATIONS	PTO USE
24. ☐ Basic national fee	$300	$ $0.00	
25. ☐ Examination fee			
If International preliminary examination report prepared by USPTO and all claims satisfy provisions of PCT Article 33(1)-(4)	$100	$ $0.00	
All other situations	$200		
26. ☐ Search fee			
Search fee (37 CFR 1.445(a)(2)) has been paid on the international application to the USPTO as an International Searching Authority	$100		
International Search Report prepared and provided to the Office	$400		
All other situations	$500	$ $0.00	
TOTAL OF 24, 25 and 26 =		$ $0.00	

☐ Additional fee for specification and drawings filed in paper over 100 sheets (excluding sequence listing or computer program listing filed in an electronic medium). The fee is $250 for each additional 50 sheets of paper or fraction thereof.

Total Sheets	Extra Sheets	Number of each additional 50 or fraction thereof (round up to a whole	RATE	
- 100 =	0 /50 =	0	x $250.00	$ $0.00

Surcharge of **$130.00** for furnishing the oath or declaration later than months from the earliest claimed priority date (37 CFR 1.492(e)). $ $130.00

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	- 20 =	0	x $50.00	$ $0.00
Independent claims	- 3 =	0	x $200.00	$ $0.00
MULTIPLE DEPENDENT CLAIMS (if applicable) ☐			+ $360.00	$ $0.00
TOTAL OF ABOVE CALCULATIONS =				$ $130.00
☐ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.				$ $0.00
SUBTOTAL =				$ $130.00
Processing fee of **$130.00** for furnishing the English translation later than 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				$ $0.00
TOTAL NATIONAL FEE =				$ $130.00
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40 per property +				$ $40.00
TOTAL FEES ENCLOSED =				$ $170.00
07/11/2005 ATRAN1 00000081 10518016				Amount to be $
01 FC:1617 130.00 OP				Amount to be $

a. ☒ A check in the amount of $ **$170.00** to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Director is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **19-4375**. A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 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 International Application to pending status.

SEND ALL CORRESPONDENCE TO:

Thomas P. Pavelko, Esquire
STEVENS, DAVIS, MILLER & MOSHER, L.L.P.
1615 L Street, N.W., Suite 850
Washington, D.C. 20036
Telephone: (202) 785-0100
Facsimile: (202) 408-5200 or (202) 408-5088

SIGNATURE

Thomas P. Pavelko

NAME

31,689

REGISTRATION NUMBER

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application

Amar LULLA et al.

Serial No.: To be assigned (National Stage of PCT/GB03/02557 filed June 13, 2003)

Filed: December 14, 2004

For: COMBINATION OF AZELASTINE AND STEROIDS

PRELIMINARY AMENDMENT

Mail Stop Patent Application
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Prior to the calculation of the filing fee, please amend the above-identified application as follows:

IN THE SPECIFICATION

Please add the following paragraph on a new line after the title:

This application is a §371 National Stage Application of International Application No. PCT/GB03/02557, filed on 13 June 2003, claiming the priority of Great Britain Patent Application No. 0213739.6 filed on 14 June 2002, the entire disclosures of which are herein incorporated by reference in their entirety.

IN THE ABSTRACT

After the last page of claims, insert on a new page the Abstract shown on the attached sheet (ATTACHMENT I).

IN THE CLAIMS

Please cancel claim 43.

1. (Currently Amended) A pharmaceutical formulation which comprises azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, and a steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof~~, preferably the formulation being in a form suitable for nasal or ocular administration~~.

2. (Original) A pharmaceutical formulation according to claim1, wherein said azelastine is present as azelastine hydrochloride.

3. (Currently Amended) A formulation according to claim 1 ~~or 2~~, wherein the steroid is beclomethasone or a pharmaceutically acceptable ester thereof, mometasone or a pharmaceutically acceptable ester thereof, fluticasone or a pharmaceutically acceptable ester thereof, budesonide or cyclosenide, in any chiral form or mixture.

4. (Original) A formulation according to claim 3, wherein the steroid is beclomethasone propionate, mometasonefuroate, mometasone furoate monohydrate, fluticasone propionate or fluticasone valerate.

5. (Currently Amended) A formulation according to claim 1 ~~any of claims 1 to 4~~, which contains the steroid in an amount from about 50 micrograms/ml to about 5 mg/ml of the formulation.

6. (Currently Amended) A formulation according to claim 1 ~~any of claims 1 to 5~~, wherein the formulation has a particle size of less than about 10 μm~~, preferably less than 5μn~~.

7. (Currently Amended) A formulation according to claim 1 ~~any of claims 1 to 6~~, which is a suspension containing 0.0005 to 2% (weight/weight of the formulation) of azelastine or a pharmaceutically acceptable salt of azelastine, and from 0.5 to 1.5% (weight/weight of the formulation) of said steroid.

8. (Original) A formulation according to claim 7, which contains from 0.001 to 1% (weight/weight of the formulation) azelastine, or salt thereof, and from 0.5% to 1.5% (weight/weight of the formulation) steroid.

9. (Currently Amended) A formulation according to claim 1 ~~any of claims 1 to 8~~, which also contains a surfactant.

10. (Original) A formulation according to claim 9, wherein the surfactant comprises a polysorbate or poloxamer surfactant.

11. (Currently Amended) A formulation according to claim 9 ~~or 10~~, which contains from about 50 micrograms to about 1 milligram of surfactant per ml of the formulation.

12. (Currently Amended) A formulation according to claim 1 ~~any of claims 1 to 11~~, which also contains an isotonic agent.

13. (Original) A formulation according to claim 12, wherein the isotonic agent comprises sodium chloride, saccharose, glucose, glycerine, sorbitol or 1,2-propylene glycol.

14. (Currently Amended) A formulation according to claim 1 ~~any of claims 1 to 13~~, which also contains at least one additive selected from the group consisting of a buffer, a preservative, ~~and~~ a suspending agent and a ~~or~~ thickening agent.

15. (Original) A formulation according to claim 14, wherein said preservative is selected from edetic acid and its alkali salts, lower alkyl p-hydroxybenzoates, chlorhexidine,

phenyl mercury borate, or benzoic acid or a salt, a quaternary ammonium compound, or sorbic acid or a salt thereof.

16. (Currently Amended) A formulation according to claim 14 ~~or 15~~, wherein the suspending agent or thickening agent is selected from cellulose derivatives, gelatin, polyvinylpyrrolidone, tragacanth, ethoxose (water soluble binding and thickening agents on the basis of ethyl cellulose), alginic acid, polyvinyl alcohol, polyacrylic acid, or pectin.

17. (Currently Amended) A formulation according to claim 14 ~~any of claims 14,15 or 16~~, wherein the buffer comprises a citric acid-citrate buffer.

18. (Currently Amended) A formulation according to claim 14 ~~any of claims 14,15, 16 or 17~~, wherein the buffer maintains the pH of the aqueous phase at from 3 to 7, preferably 4.5 to about 6.5.

19. (Currently Amended) A formulation according to claim 1 ~~any of claims 1 to 18~~, which is an aqueous suspension or solution.

20. (Currently Amended) A formulation according to claim 1 ~~19~~, which is in the form of an aerosol, an ointment, eye drops, nasal drops, a nasal spray, ~~or~~ an inhalation solution and other forms suitable for nasal or ocular administration.

21. (Original) A formulation according to claim 20, which is in the form of nasal drops or nasal spray.

22. (Original) A formulation according to claim 20, which is in the form of an aerosol.

23. (Original) A pressure packing having a dosage or metering valve, which contains a formulation according to claim 22.

24. (Original) A MDI which includes a pressure packing according to claim 23.

25. (Currently Amended) A formulation according to claim 1 ~~any of claims 1 to 19~~, which is in the form of an insufflation powder.

26. (Currently Amended) A pharmaceutical product according to claim 1, comprising (i) azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, provided in an aerosol formulation preferably together with a propellant typically suitable for MDI delivery, and (ii) at least one steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, provided in an aerosol formulation preferably together with a propellant typically suitable for MDI delivery, as a combined preparation for simultaneous, separate or sequential use in the treatment of conditions for which administration of one or more anti-histamine and/or one or more steroid is indicated.

27. (Currently Amended) An aerosol formulation preferably suitable for MDI delivery comprising the formulation of claim 1 ~~(i) azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, and (ii) at least one steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof~~, together with a propellant.

28. (Original) A pharmaceutical product comprising (i) azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, provided as an insufflation powder, and (ii) at least one steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, provided as an insufflation powder, as a combined preparation for simultaneous, separate or sequential use in the treatment of

conditions for which administration of one or more anti-histamine and/or one or more steroid is indicated.

29. (Original) An insufflation powder formulation comprising (i) azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, and (ii) at least one steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, together with a pharmaceutically acceptable carrier or excipient therefor.

30. (Currently Amended) A pharmaceutical product comprising the formulation according to claim 1, wherein (i) azelastine, or a pharmaceutically acceptable salt thereof, and (ii) wherein at least one steroid is selected from the group consisting of beclomethasone, fluticasone, mometasone and pharmaceutically acceptable esters thereof, as a combined preparation with said azelastine for simultaneous, separate or sequential use in the treatment of conditions for which administration of one or more anti-histamine and/or one or more steroid is indicated.

31. (Currently Amended) A pharmaceutical formulation according to claim 1, wherein said ~~comprising (i) azelastine, or a pharmaceutically acceptable salt thereof, and (ii)~~ at least one steroid is selected from the group consisting of beclomethasone, fluticasone, mometasone and pharmaceutically acceptable esters thereof, together with a pharmaceutically acceptable carrier or excipient therefor.

32. (Currently Amended) The formulation of claim 3 in the form of a [[A]] nasal spray comprising azelastine, or a pharmaceutically acceptable salt thereof, together with mometasone either as mometasone free base or as mometasonefuroate, and a pharmaceutically acceptable carrier or excipient therefor.

33. (Currently Amended) A pharmaceutical product comprising the formulation according to claim 1, wherein said azelastine is azelastine hydrochloride and said steroid is beclomethasone dipropionate, as a combined preparation for simultaneous, separate or sequential use in the treatment of conditions for which administration of one or more anti-histamine and/or one or more steroid is indicated.

34. (Currently Amendedl) A pharmaceutical formulation according to claim 1, wherein said azelastine is ~~comprising~~ azelastine hydrochloride and said steroid is beclomethasone dipropionate, together with a pharmaceutically acceptable carrier or excipient therefor.

35. (Currently Amended) A pharmaceutical product comprising the pharmaceutical formulation of claim 1, wherein said azelastine is azelastine hydrochloride and said steroid is fluticasone propionate, as a combined preparation for simultaneous, separate or sequential use in the treatment of conditions for which administration of one or more anti-histamine and/or one or more steroid is indicated.

36. (Currently Amended) A pharmaceutical formulation according to claim 1, wherein said azelastine is ~~comprising~~ azelastine hydrochloride and said steroid is fluticasone propionate, together with a pharmaceutically acceptable carrier or excipient therefor.

37. (Currently Amended) A pharmaceutical product comprising the pharmaceutical formulation of claim 1, wherein said azelastine is azelastine hydrochloride and said steroid is fluticasone valerate, as a combined preparation for simultaneous, separate or sequential use in the treatment of conditions for which administration of one or more anti-histamine and/or one or more steroid is indicated.

38. (Currently Amended) A pharmaceutical formulation according to claim 1, wherein said azelastine is ~~comprising~~ azelastine hydrochloride and said steroid is fluticasone valerate, together with a pharmaceutically acceptable carrier or excipient therefor.

39. (Currently Amended) A pharmaceutical product comprising the pharmaceutical formulation of claim 1, wherein said steroid is azelastine hydrochloride and said steroid is mometasonefuroate, as a combined preparation for simultaneous, separate or sequential use in the treatment of conditions for which administration of one or more anti-histamineand/or one or more steroid is indicated.

40. (Currently Amended) A pharmaceutical formulation according to claim 1, wherein said azelastine is ~~comprising~~ azelastine hydrochloride and said steroid is mometasonefuroate, together with a pharmaceutically acceptable carrier or excipient therefor.

41. (Currently Amended) A pharmaceutical product comprising the pharmaceutical formulation of claim 1, wherein said azelastine is azelastine hydrochloride and said steroid is mometasonefuroate monohydrate, as a combined preparation for simultaneous, separate or sequential use in the treatment of conditions for which administration of one or more anti-histamine and/or one or more steroid is indicated.

42. (Currently Amended) A pharmaceutical formulation according to claim 1, wherein said azelastine is ~~comprising~~ azelastine hydrochloride and said steroid is mometasonefuroate monohydrate, together with a pharmaceutically acceptable carrier or excipient therefor.

43. Cancelled

44. (Currently Amended) A process of preparing a pharmaceutical product according to claim 26 ~~any of claims 26, 28, 30, 33, 35,37, 39 or 41~~, which process comprises providing (i) azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, and (ii) at least one steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, as a combined preparation for simultaneous, separate or sequential use in the treatment of conditions for which administration of one or more antihistamine and/or one or more steroid is indicated.

45. (Currently Amended) A process of preparing a pharmaceutical formulation according to claim 1 ~~any of claims 1 to 22, 27, 29, 31, 32, 34, 36, 38, 40, 42 or 43~~, which process comprises admixing a pharmaceutically acceptable carrier or excipient with azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, and at least one steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.

46. (Currently Amended) A method for the prophylaxis or treatment in a mammal, such as a human, of conditions for which administration of one or more anti-histamine and/or one or more steroid is indicated, which method comprises administration of a therapeutically effective amount of a pharmaceutical product according to claim 26 ~~any of claims 26, 28, 30, 33, 35, 37, 39 or 41~~, as a combined preparation for simultaneous, separate or sequential use in the treatment of such conditions.

47. (Currently Amended) A method for the prophylaxis or treatment in a mammal, such as a human, of conditions for which administration of one or more anti-histamine and/or one or more steroid is indicated, which method comprises administration of a therapeutically

effective amount of a pharmaceutical formulation according to claim 1 ~~any of claims 1 to 22, 27, 29, 31, 32, 34, 36, 38, 40, 42 or 43~~.

48. (Currently Amended) For use in the manufacture of a medicament for the prophylaxis or treatment in a mammal, such as a human, of conditions for which administration of one or more antihistamine and/or one or more steroid is indicated, a pharmaceutical product according to claim 26 ~~any of claims 26, 28, 30, 33, 35, 37, 39 or 41~~, as a combined preparation for simultaneous, separate or sequential use in the treatment of such conditions.

49. (Currently Amended) A method of treating irritation or disorders of the nose or eye which comprises applying either directly to nasal tissues or to the conjunctival sac of the eyes, as appropriate, a pharmaceutical product according to claim 26 ~~any of claims 26, 28, 30, 33, 35, 37, 39 or 41, or a pharmaceutical formulation according to any of claims 1 to 22, 27, 29, 31, 32, 34, 36, 38, 40, 42 or 43~~.

50. (Currently Amended) A method of treating airway disorders, comprising administering by nebulization to surfaces of the airway a treatment-effective amount of a product or formulation as defined in claim 1 ~~the preceding claims~~.

51. (New) A method of treating irritation or disorders of the nose or eye which comprises applying either directly to nasal tissues or to the conjunctival sac of the eyes, as appropriate, a pharmaceutical formulation of claim 1.

52. (New) A method of treating airway disorders, comprising administering by nebulization to surfaces of the airway a treatment-effective amount of a product according to claim 26.

REMARKS

The claims have been amended to delete the multiple dependent claim status. No new matter is presented by the above amendments. Early and favorable consideration of this application is respectfully requested.

Respectfully submitted,

Date: Dec 14, 2004 By: _____

Thomas P. Pavelko
Registration No. 31,689

TPP/pgw
ATTORNEY DOCKET NO. TPP31573

STEVENS, DAVIS, MILLER & MOSHER, L.L.P.
1615 L STREET, N.W., SUITE 850
WASHINGTON, D.C. 20036
TEL. 202-785-0100 / FAX. 202-785-0200

ATTACHMENT I – Abstract

A pharmaceutical product or formulation, which comprises azelastine or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, and a steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, preferably the product or formulation being in a form suitable for nasal or ocular administration.

APPLICATION DATA SHEET

TITLE OF INVENTION	COMBINATION OF AZELASTINE AND STEROIDS

APPLICATION TYPE: Utility

CORRESPONDENCE ADDRESS:
Customer Number: 24257 *24257*

PRIORITY DATA:
Doc. No.: 0213739.6; Country - GB; Date: 14 June 2002

ATTORNEY INFORMATION:
Name: Thomas P. Pavelko
Registration No.: 31,689

ATTORNEY DOCKET NUMBER:
TPP 31753

INVENTORS INFORMATION:

Applicant Authority Type:	Inventor
Citizenship:	Indian
Name Prefix:	Mr.
Given Name:	Amar
Family Name:	LULLA
City of Residence:	Mumbai
Country of Residence:	India
Address - 1 of Mailing Address:	103 Maker Towers 'L', Cuff Parade, Colaba
City of Mailing Address:	Mumbai
Postal Code of Mailing Address:	400 005
Country of Mailing Address:	INDIA

INVENTORS INFORMATION:

Applicant Authority Type:	**Inventor**
Citizenship:	**Indian**
Name Prefix:	**Ms.**
Given Name:	**Geena**
Family Name:	**MALHOTRA**
City of Residence:	**Mumbai**
Country of Residence:	**India**
Address - 1 of Mailing Address:	**8 Anderson House, Opp Mazgaon Dock P.O., Mazgaon**
City of Mailing Address:	**Mumbai**
Postal Code of Mailing Address:	**400 010**
Country of Mailing Address:	**INDIA**

ASSIGNEE:

Organization:	**CIPLA LIMITED**
Address:	**289 Bellasis Road, Mumbai Central**
City:	**Mumbai**
Postal Code:	**400 008**
Country:	**India**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of

Amar LULLA et al.

Serial No.: To be assigned (National Phase of PCT/GB03/02557 filed June 13, 2003)

Filed: December 14, 2004

For: COMBINATION OF AZELASTINE AND STEROIDS

NOTICE OF CLAIM FOR PRIORITY

Mail Stop Patent Application
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

The benefit of the filing date of the following prior foreign application filed in the following foreign country is hereby requested for the above-identified application and the priority provided in 35 USC 119 is hereby claimed:

Great Britain Appln. No. 0213739.6, Filed 14 June 2002 .

It is requested that the file of this application be marked to indicate that the requirements of 35 USC 119 have been fulfilled and that the Patent and Trademark Office kindly acknowledge receipt of this document.

Respectfully submitted,

Date: Dec 14, 2004 By: _____
Registration No. 31,674

TPP/pgw
ATTORNEY DOCKET NO. TPP31753

STEVENS, DAVIS, MILLER & MOSHER, L.L.P.
1615 L Street, N.W., Suite 850
Washington, D.C. 20036
Tel: 202-408-5100 / Fax. 202-785-0200

PCT/GB2003/002557

Rec'd PCT/PTO 14 DEC 2004

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

INVESTOR IN PEOPLE

RECD 25 JUL 2003
WIPO PCT

BEST AVAILABLE COPY

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

Signed P. Mahoney

Dated 10 July 2003

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN
COMPLIANCE WITH
RULE 17.1(a) OR (b)

Patent Form 1/77

Patents Act 1977
(Rule 16)

The Patent Office

17J E726041-9 000180
P01/7700 0.00-0213739.6

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

14 JUN 2002
HAND DELIVERED BY HAND

The Patent Office

Cardiff Road
Newport
South Wales
NP9 1RH

1. Your reference — CPW/20632 — 14 JUN 2002

2. Patent application number *(The Patent Office will fill in this part)* — 0213739.6

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

CIPLA LIMITED

289 BELLASIS ROAD
MUMBAI CENTRAL
MUMBAI 400 008
INDIA

Patents ADP number *(if you know it)* 7739162001

If the applicant is a corporate body, give the country/state of its incorporation — INDIA

4. Title of the invention — PHARMACEUTICAL COMPOSITIONS

5. Name of your agent *(if you have one)*

A A THORNTON & CO

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

235 HIGH HOLBORN
LONDON WC1V 7LE

Patents ADP number *(if you know it)* 0000075001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

YES

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	7
Claim(s)	3
Abstract	
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	ONE
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature A. A. Thornton & Co. Date 14/6/02 14th June 2002

12. Name and daytime telephone number of person to contact in the United Kingdom: Philip A. Curtis - 020 7440 6860

Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

a) *If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.*

b) *Write your answers in capital letters using black ink or you may type them.*

c) *If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.*

d) *If you have answered 'Yes' Patents Form 7/77 will need to be filed.*

e) *Once you have filled in the form you must remember to sign and date it.*

f) *For details of the fee and ways to pay please contact the Patent Office.*

PHARMACEUTICAL COMPOSITIONS

This invention relates to pharmaceutical compositions. More particularly this invention relates to pharmaceutical compositions useful for preventing or minimising allergic reactions. More particularly, but not exclusively, this invention relates to pharmaceutical compositions for nasal and ocular use.

Such allergic reactions commonly comprise the allergy-related and vasomotor-related symptoms and the rhinovirus-related symptoms.

It is known to use antihistamines in nasal sprays and eye drops to treat allergy-related conditions. Thus, for example, it is known to use the antihistamine azelastine (usually as the hydrochloride salt) as a nasal spray against seasonal or perennial allergic rhinitis, or as eye drops against seasonal and perennial allergic conjunctivitis.

It is also known to treat these conditions using a corticosteroid, which will suppress nasal and ocular inflammatory conditions. Among the corticosteroids known for nasal use are, for example, beclomethasone, mometasone, fluticasone, budesonide and cyclosenide. Corticosteroids known for ocular anti-inflammatory use include betamethasone sodium, dexamethasone sodium and prednisolone acetate, for example.

It would be highly desirable, however, to provide a treatment that combines the effects of anti-histamine treatments and steroid treatments, in a pharmaceutically acceptable composition, which is tolerated *in situ*, without significantly disrupting the potency of the constituent pharmaceuticals.

We have now found that, very surprisingly, azelastine (4-[(4-Chlorophenyl)methyl]-2-(hexahydro-1-methyl-1H-azepin-4-yl)-1(2H)-phthalazinone) , or a salt thereof, can advantageously be combined with a steroid to provide a stable, very effective combination composition for nasal or ocular treatment. The combination provides, in a single administration, the antihistaminic properties of azelastine and the anti-inflammatory (and/or other) properties of the steroid, without any significant interference between the two, or adverse reaction *in situ*.

In one aspect the invention provides a pharmaceutical composition comprising azelastine or a salt thereof and a steroid, preferably a corticosteroid, the composition being in a form suitable for administration nasally or ocularly.

The preferred forms of compositions of the invention are nasal drops, eye drops, nasal sprays, nasal inhalation solutions or aerosols or insufflation powders.

Preferred embodiments of the invention comprise stable aqueous solutions of azelastine or one or more of its salts, in combination with steroids which may be beclomethasone, mometasone, fluticasone, budesonide or cyclosenide, which can be used in the form of inhalation solution, pressurized aerosol, eye drops or nasal drops, and in a particular preferred embodiment, in the form of a spray (preferably a nasal spray). The spray can, for example, be formed by the use of a conventional spray-squeeze bottle or a pump vaporizer. In addition, it is also possible to use compressed gas aerosols. In a preferred embodiment, 0.03 to 3 mg of azelastine base and 0.05 to 0.15 mg of the steroid should be released per individual actuation.

The compositions preferably contain a preservative and/or stabilizer. These include, for example: ethylene diamine tetra-acetic acid (edetic acid) and its alkali salts (for example dialkali salts such as disodium salt, calcium salt, calcium-sodium salt), lower alkyl p-hydroxybenzoates, chlorohexidine (for example in the form of the acetate or gluconate), phenyl mercury borate. Other suitable preservatives are: pharmaceutically useful quaternary ammonium compounds, for example cetylpyridinium chloride, tetradecyltrimethyl ammonium bromide, generally known as "cetrimide", benzyldimethyl-[2-[2-[p-(1,1,3,3-tetramethyl-butyl)phenoxy]ethoxy]-ammonium chloride, generally known as "benzethonium chloride" and myristyl-:-picolinium chloride. Each of these compounds may be used in a concentration of 0.002 to 0.05%, for example 0.02% (weight/volume in liquid formulations, otherwise weight/weight). Preferred preservatives among the quaternary ammonium compounds are, however, alkylbenzyl dimethyl ammonium chloride and mixtures thereof, for example the compounds generally known as "benzalkonium chloride".

The total amounts of preservatives in the formulations (solutions, ointments, etc.) is preferably from 0.001 to 0.10g, preferably 0.01g per 100ml of solution/suspension or 100g of formulation.

In the case of preservatives, the following amounts of individual substances can, for example, be used: thimero sal 0.002-0.02%; benzalkonium chloride 0.002 to 0.02% (in combination with thimero sal the amount of thimero sal is, for example =0.002 to 0.005%;); chlorhexidine acetate or gluconate 0.01 to 0.02%; phenyl mercuric/nitrate, borate, acetate 0.002-0.004%; p-hydroxybenzoic acid ester (for example, a mixture of the methyl ester and propyl ester in the ratio 7:3): preferably 0.05-0.15, more preferably 0.1%.

The preservative used is preferably a combination of edetic acid (for example, as the disodium salt) and benzalkonium chloride. In this combination, the edetic acid is preferably used in a concentration of 0.05 to 0.1%, benzalkonium chloride preferably being used in a concentration of 0.005 to 0.05%, more preferably 0.01%.

In the case of solutions/suspensions reference is always made to percent by weight/volume, in the case of solid or semi-solid formulations to percent by weight/weight of the formulation.

Further auxiliary substances which may, for example, be used for the formulations of the invention are: polyvinyl pyrrolidone, sorbitan fatty acid esters such as sorbitan trioleate, polyethoxylated sorbitan fatty acid esters (for example polyethoxylated sorbitan trioleate), sorbimacrogol oleate, synthetic amphotensides (tritons), ethylene oxide ethers of octylphenolformaldehyde condensation products, phosphatides such as lecithin, polyethoxylated fats, polyethoxylated oleotriglycerides, polyethoxylated fatty alcohols. In this context, polyethoxylated means that the relevant substances contain polyoxyethylene chains, the degree of polymerisation of which is generally between 2 to 40, in particular between 10 to 20. These substances are preferably used to improve the solubility of the azelastine component.

It is optionally possible to use additional isotonization agents. Isotonization agents which may, for example, be used are: saccharose, glucose, glycerine, sorbitol, 1,2-propylene glycol, NaCl.

The isotonization agents adjust the osmotic pressure of the formulations to the same osmotic pressure as nasal secretion. For this purpose these substances are in each case to be used in such amount that, for example, in the case of a solution, a reduction in the freezing point of 0.50 to 0.56 degree C is attained in comparison to pure water.

In Example 1, it is possible to use instead of NaCl per 100 ml of solution, for example: Glucose $1H_2O$ 3.81g; saccharose 6.35g; glycerine 2.2g; 1,2-propylene glycol 1.617g; sorbitol 3.84g (in the case of mixtures of these substances correspondingly less may optionally be used).

Moreover, it is possible to add thickening agents to the solutions to prevent the solution from flowing out of the nose too quickly and to give the solution a viscosity of about 1.5 to 3, preferably 2 mPa.

Such thickening agents may, for example, be: cellulose derivatives (for example cellulose ether) in which the cellulose-hydroxy groups are partially etherified with lower unsaturated aliphatic alcohols and/or lower unsaturated aliphatic oxyalcohols (for example methyl cellulose, carboxymethyl cellulose, hydroxypropylmethylcellulose), gelatin, polyvinylpyrrolidone, tragacanth, ethoxose (water soluble binding and thickening agents on the basis of ethyl cellulose), alginic acid, polyvinyl alcohol, polyacrylic acid, pectin and equivalent agents. Should these substances contain acid groups, the corresponding physiologically acceptable salts may also be used.

In the event of the use of hydroxypropyl cellulose, 0.1% by weight of the formulation, for example, is used for this purpose.

In the event of the use of Avicel RC 591 or CL11, 0.65-3.0% by weight of the composition, for example, is used for the purpose.

It is also possible to add to the formulations buffer substances such as citric acid/sodium hydrogensulphate borate buffer, phosphates (sodium hydrogenorthophosphate, disodium hydrogenphosphate), trometamol or equivalent conventional buffers in order, for example, to adjust the formulations to a pH value of 3 to 7, preferably 4.5 to 6.5.

The amount of citric acid is, for example, 0.01 to 0.14g, preferably 0.04 to 0.05g, the amount of disodium hydrogenphosphate 0.1 to 0.5g, preferably 0.2 to 0.3g per 100 ml of solution. The weights given relate in each case to the anhydrous substances.

In the case of solutions and suspensions, the maximum total concentration of active agent and buffer is preferably less than 5%, in particular less than 2% (weight/volume).

For the nasal application a solution or suspension is preferably used which is applied as an aerosol, i.e. in the form of a fine dispersion in air or in another conventional carrier gas, for example by means of a conventional pump vaporizer.

Application as a dosage aerosol is, however, also possible. Dosage aerosols are defined as being pressure packings which contain the azelastine or its salts in combination with steroid, in the form of a solution or suspension in a so-called propellant. The propellant may be a pressurized liquid chlorinated, fluorinated hydrocarbon or mixtures of various chlorinated, fluorinated hydrocarbons as well as propane, butane, isobutene or mixtures of these among themselves or with chlorinated, fluorinated hydrocarbons which are gaseous at atmospheric pressure and room temperature. Hydrofluorocarbons (HFCs), such as HFC 134a, can also be used, if desired. The pressure packing has a dosage valve which, on actuation, releases a defined amount of the solution or suspension of the medicament. The subsequent very sudden vaporization of the propellant tears the solution or suspension of azelastine into the finest droplets or minute particles which can be sprayed in the nose or which are available for inspiration into the nose. Certain plastic applicators may be used to actuate the valve and to convey the sprayed suspension into the nose.

In the case of application as an aerosol, it is also possible to use a conventional adapter.

In the case of insufflatable powder, the maximum particle size of the substance preferably does not exceed 10μm. Azelastine or its salts and the steroid may be mixed with inert carrier substances or drawn up onto inert carrier substances. Carrier substances which may, for example, be used are: sugars such as glucose, saccharose, lactose and fructose. Also starches or starch derivatives, oligosaccharides such as dextrins, cyclodextrins and their derivatives, polyvinylpyrrolidone, alginic acid, tylose, silicic acid, cellulose, cellulose derivatives (for example cellulose ether), sugar alcohols such as mannitol or sorbitol, calcium carbonate, calcium phosphate, etc.

In one embodiment, the steroid has a particle size of less than about 10μm, preferably less than 5 μm.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The invention is illustrated by the following examples.

EXAMPLE 1

Nasal spray or nasal drops with 0.1% azelastine hydrochloride as active ingredient and steroid 0.1%

S.NO.	NAME OF INGREDIENTS	OUANTITY %w/v
1. *	Azelastine hydrochloride	0.1%
2.	Steroid	0.1%
3.	Disodium edetate	0.005%
4.	Sodium chloride	0.9%
5.	Benzalkonium chloride	0.001%
6.	Avicel RC 591	1.2%
7.	Citric acid monohydrate	0.2%
8.	Disodium hydrogen phosphate dodecahydrate	0.1%
9.	Purified water	

EXAMPLE 2

Dosage aerosol giving off 0.5 mg of azelastine hydrochloride and 50 micrograms of Beclomethasone dipropionate freon solvate per stroke.

About 8.0 kg of a mixture of 70 parts by weight of difluorodichloromethane and 30 parts by weight of 1,2dichlorotetrafluoroethane are cooled to about –55 degree C in an appropriate cooling vessel. A mixture of 0.086 kg of pre-cooled sorbitantrioleate and 0.8600 kg of pre-cooled trichlorofluoromethane are dissolved with stirring into the mixture at –55 degrees C, 0.0688 kg of micronized azelastine hydrochloride, 0.00688 kg of Beclomethasone dipropionate freon solvate and 0.0688 kg of micronized lactose are then incorporated in portions into the solution thereby obtained with intensive stirring. The total weight of the suspension thereby obtained is made up to 9.547 kg through addition of more of the mixture of 70 parts by weight of difluorodichloromethane and 30 parts by weight of 1,2-dichlorotetrafluoroethane cooled to about –55 degree C.

Following closure of the cooling vessel the suspension is again cooled to about -55 degrees C under intensive stirring. It is then ready to be filled.

CLAIMS:

1 A pharmaceutical composition which comprises azelastine or a salt thereof, and a steroid, the composition being in a form suitable for nasal or ocular administration.

2 A composition according to claim 1, which is an aqueous suspension or solution.

3 A composition according to claim 1 or 2, which is in the form of an aerosol, an ointment, eye drops, nasal drops, a nasal spray or an inhalation solution.

4 A composition according to claim 1, which is in the form of an insufflation powder.

5 A composition according to any of claims 1 to 4, wherein the steroid is beclomethasone or an ester thereof, mometasone or an ester thereof, fluticasone or an ester thereof, budesonide or cyclosenide, in any chiral form or mixture.

6 A composition according to claim 5, wherein the steroid is beclomethasone propionate, mometasone furoate or fluticasone propionate.

7 An composition according to any of claims 1 to 6, which contains the steroid in an amount from about 50 micrograms/ml to about 5 mg/ml of the composition.

8 A composition according to any of claims 1 to 7, which is a suspension containing 0.0005 to 2% (weight/weight of the composition) of azelastine or a pharmaceutically acceptable salt of azelastine, and from 0.5 to 1.5% (weight/weight of the composition) of said steroid.

9 A composition according to claim 8, which contains from 0.001 to 1% (weight/weight of the composition) azelastine, or salt thereof, and from 0.5% to 1.5% (weight/weight of the composition) steroid.

10 A composition according to any of claims 1 to 9, wherein the composition has a particle size of less than about 10μm, preferably less than 5 μm.

11 A composition according to any of claims 1 to 10, which also contains a surfactant.

12 A composition according to claim 11, wherein the surfactant comprises a polysorbate or poloxamer surfactant.

13 A composition according to claim 10 or 11, which contains from about 50 micrograms to about 1 milligram of surfactant per ml of the composition.

14 A composition according to any of claims 1 to 13, which also contains an isotonic agent.

15 A composition according to claim 14, wherein the isotonic agent comprises sodium chloride, saccharose, glucose, glycerine, sorbitol or 1,2-propylene glycol.

16 A composition according to any of claims 1 to 15, which also contains at least one of a buffer, a preservative and a suspending or thickening agent.

17 A composition according to claim 16, wherein said preservative is selected from edetic acid and its alkali salts, lower alkyl p-hydroxybenzoates, chlorohexidine, phenyl mercury borate, or benzoic acid or a salt, a quaternary ammonium compound, or sorbic acid or a salt thereof.

18 A composition according to claim 16 or 17, wherein the suspending agent or thickening agent is selected from cellulose derivatives, gelatine, polyvinylpyrrolidone, tragacanth, ethoxose (water soluble binding and thickening agents on the basis of ethyl cellulose), alginic acid, polyvinyl alcohol, polyacrylic acid, or pectin.

19 A composition according to claim 16, 17 or 18, wherein the buffer comprises a citric acid-citrate buffer.

20 A composition according to claim 16, 17, 18 or 19, wherein the buffer maintains the pH of the aqueous phase at from 3 to 7, preferably 4.5 to about 6.5.

21 An aqueous pharmaceutical composition substantially as herein described in Example 1 or 2.

22 A method of treating irritation or disorders of the nose and eye which comprises applying directly to nasal tissues or to the conjunctival sac of the eyes, a medicament which contains a member selected from the group consisting of azelastine and its pharmaceutically acceptable salts, in combination with a steroid.

23 A method according to claim 22, in which the medicament is a composition as claimed in any of claims 1 to 21.

24 A method of treating airway disorders, comprising administering by nebulization to surfaces of the airway a treatment-effective amount of a composition as claimed in any of claims 1 to 21.

U.S NATIONAL STAGE WORKSHEET (DO/EO)

U.S. APPL. NO. 10/518016 INTERNATIONAL APPL. GB03/02557

APPLICATION FILED BY: 20 MOS., ____ OR 30 MOS., ____ SCREENED BY 14 Dec 2004

Francine Young
PCT International Division

INTERNATIONAL APPLICATION PAPERS IN THE APPLICATION FILE:

- / International application
- ___ Article 19 amendments
- / Priority Document(s) No. /
- ___ Request Form PCT/RO/101
- ___ PCT/IB/302
- ___ PCT/IB/304
- ___ PCT/IB/306
- ___ PCT/IB/308
- ___ PCT/IB/331
- / OTHER PCT/IB/____
- / PCT/IPEA/409 also 416 EP
- ___ 409 annexes to IPER
- / PCT/ISA/210 (Search report) EP
- ___ Search report References
- ___ Other Papers filed

WIPO PUBLICATION
PUBLICATION NO. *WO* 03/105856
PUBLICATION DATE 24 Dec 2003
PUBLICATION LANG., English
NOT PUBLISHED
_____ U.S. only _____ Requested

RECEIVED FROM THE APPLICANT: (other than checked above)

- / National application basic fee paid
- ___ Express Processing Requested
- ___ Translation of the International Application
- / Used the IB copy of the IA
- ___ Description
- ___ Claims____
- ___ Drawings___
- ___ Foreign Language in drawing
- ___ Article 19 Amendments
- ___ Amendment used in application
- ___ Article 34 Amendment
- ___ Amendment used in application
- ___ DNA
- ___ 1194 transaction done
- / Preliminary Amendment(s) filed 14 Dec 2004
- ____ second submission_____
- ____ Information Disclosure Statement_____
- ____ second submission_____
- ____ Assignment
- _____Forward to Assignment Branch
- _____Substitute Specification_____
- ____ Small Entity Statement _____
- type _____
- / Oath/Declaration (date submitted 6 July 2005
- ___ Not executed
- / Executed
- ____ Power of Attorney
- ____ Change of Address

Data Sheet, Priority Claim

35 USC Receipt of Request (PTO – 1399 Transmittal Letter) 14 DEC 2004
Date Acceptable oath/declaration received 06 JUL 2005
102(e) Date 06 JUL 2005
Date complete 35 USC 371 requirements met 06 JUL 2005

DATE NOTICE COMPLETED

DO/EO 903 Notice of Acceptance
DO/EO 905 Notice of Missing Requirements 5 May 2005
DO/EO 917 Notice of A defective oath or declaration
DO/EO 916 Notice of defective response
DO/EO 913 Notice of defective translation
DO/EO 909 Notifiication of Abandonment

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)
CPW/20632		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB 03/02557	13.06.2003	14.06.2002
International Patent Classification (IPC) or both national classification and IPC		
A61K31/55		
Applicant		
CIPLA LIMITED 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 6 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 consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - 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 Rule 66.2(a)(ii) 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
07.01.2004	26.08.2004
Name and mailing address of the International preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Vandenbogaerde, A Telephone No. +49 89 2399-7874

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB 03/02557

I. Basis of the 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

1-16 as originally filed

Claims, Numbers

1-50 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. 46-47,49-50 with respect to industrial applicability

   because:

   ☒ the said international application, or the said claims Nos. 46-47,49-50 with respect to industrial applicability 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	/
	No:	Claims	1-50
Inventive step (IS)	Yes:	Claims	/
	No:	Claims	1-50
Industrial applicability (IA)	Yes:	Claims	1-45, 48: YES / 46-47,49-50: see separate sheet
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 46-47 and 49-50 relate 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).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO 97 01337 A (MCNEIL PPC INC) 16 January 1997 (1997-01-16)

D2: EP-A-0 780 127 (PROCTER & GAMBLE) 25 June 1997 (1997-06-25)

D3: DATABASE MEDLINE [Online] US NATIONAL LIBRARY OF MEDICINE (NLM), BETHESDA, MD, US; 2000 PORTMANN D ET AL: '[Acceptability of local treatment of allergic rhinitis with a combination of a corticoid (beclomethasone) and an antihistaminic (azelastine)]' Database accession no. NLM11233712 XP002252974 & REVUE DE LARYNGOLOGIE - OTOLOGIE - RHINOLOGIE. FRANCE 2000, vol. 121, no. 4, 2000, pages 273-279, ISSN: 0035-1334

D4: BUSSE W W ET AL: 'CORTICOSTEROID-SPARING EFFECT OF AZELASTINE IN THE MANAGEMENT OF BRONCHIAL ASTHMA' AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE, AMERICAN LUNG ASSOCIATION, NEW YORK, NY, US, vol. 153, no. 1, 1996, pages 122-127, XP000604179

- D1 discloses (cf. page 2 line 8 - page 8 line 25) a combination of (i) a topical nasal antihistaminic, i.e. levocabastine, azelastine or azatadine, and (ii) a topical nasal steroid, i.e. beclomethasone, flunisolide, triamcinolone, dexamethasone or budesonide, as nasal spray or nasal drops for the treatment of allergic rhinitis.
- D2 describes (cf. page 2 line 34 - page 5 line 30, example 3) a combination of (i) an antihistamine possessing leukotriene inhibiting properties, i.e. cetirizine, loratadine or azelastine, and (ii) a glucocorticoid, i.e. beclomethasone, flunisolide, triamcinolone, fluticasone, mometasone or budesonide, as nasal

spray for the treatment of allergic rhinoconjunctivitis.

- D3 discloses (cf. abstract) a combination of (i) the antihistamine azelastine and (ii) the corticoid beclomethasone as nasal spray for the local treatment of seasonal or aperiodic rhinitis.
- D4 describes (page 126-127, discussion) that the combined use of (i) azelastine and (ii) corticosteroid medication in patients with asthma allowed patients to achieve a reduction in the use of inhaled corticosteroids while showing improvements in the severity of asthma symptoms and in pulmonary function.

V.1 Claims 1-43 - *Composition (for use in medicine)*: Novelty - Inventive step

V.1.1 The subject-matter of claims 1-43 relates to a composition per se or to a composition for use in medicine comprising (i) azelastine and (ii) a steroid, i.e. beclomethasone, mometasone, fluticasone, budesonide or cyclosenide.

V.1.2 The subject-matter of independent claim 1 is not novel according to Article 33(2) PCT over the teaching of D1, D2, D3 or D4.

V.1.3 Dependent claims 2-22 and 25 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step, the reasons being as follows: Document D1, which is considered to represent the most relevant state of the art, discloses (cf. page 2 line 8 - page 8 line 25) a combination of (i) a topical nasal antihistaminic, i.e. levocabastine, azelastine or azatadine, and (ii) a topical nasal steroid, i.e. beclomethasone, flunisolide, triamcinolone, dexamethasone or budesonide, as nasal spray or nasal drops for the treatment of allergic rhinitis. The problem to be solved by the present invention may therefore be regarded as the provision of alternative formulation comprising (i) azelastine and (ii) a steroid for the treatment of allergic disorders of eye and nose or airway disorders. It would be obvious to use an alternative steroid, to use alternative carriers or to prepare an alternative formulation (i.e. inhalation formulation), because no unexpected technical effect can be seen.

V.1.4 The same objections also apply to independent claims 23 (and dependent claims 24-25), 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42 and 44.

V.2 Claims 46-50 - *Therapeutical application*: Novelty - Inventive step

V.2.1 The subject-matter of claims relates to the therapeutical application of a composition comprising (i) azelastine and (ii) a steroid, i.e. beclomethasone,

mometasone, fluticasone, budesonide or cyclosenide for the treatment of conditions for which administration of one or more anti-histamine and/or one or more steroid is indicated, i.e. irritation or disorders of the nose or eye (e.g. allergic rhinitis, rhinoconjunctivis), or airway disorders (e.g. asthma).

V.2.2 The subject-matter of claims 46-50 is not novel according to Article 33(2) PCT and/or cannot be considered as involving an inventive step in the sense of Article 33(3) PCT for the same reasons as given under point V.1.

V.3 Claims 44-45 - *Process*: Novelty - Inventive step

V.3.1 The subject-matter of claims 44-45 relates to a process for preparing a pharmaceutical composition comprising (i) azelastine and (ii) a steroid, i.e. beclomethasone, mometasone, fluticasone, budesonide or cyclosenide.

V.3.2 The subject-matter of claims 46-50 is not novel according to Article 33(2) PCT and/or cannot be considered as involving an inventive step in the sense of Article 33(3) PCT, since merely standard processes are used for preparing a composition which is already known (cf. point V.1).

V.4 Industrial applicability

For the assessment of the present claims 46-47 and 49-50 on the question whether they are 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.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 December 2003 (24.12.2003)

PCT

(10) International Publication Number
WO 03/105856 A1

(51) International Patent Classification[7]: A61K 31/55, 31/56, 31/57, 31/58, 9/00, A61P 37/08, 27/14, 11/06 // (A61K 31/56, 31:55) (A61K 31/57, 31:55) (A61K 31/58, 31:55)

(21) International Application Number: PCT/GB03/02557

(22) International Filing Date: 13 June 2003 (13.06.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0213739.6 14 June 2002 (14.06.2002) GB

(71) Applicant *(for all designated States except US)*: **CIPLA LIMITED** [IN/IN]; 289 Bellasis Road, Mumbai Central, Mumbai 400 008 (IN).

(71) Applicant *(for MW only)*: **WAIN, Christopher, Paul** [GB/GB]; A.A. Thornton & Co., 235 High Holborn, London WC1V 7LE (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **LULLA, Amar** [IN/IN]; 103 Maker Towers 'L', Cuff Parade, Colaba, Mumbai 400 005 (IN). **MALHOTRA, Geena** [IN/IN]; 8 Anderson House, Opp. Mazgaon Dock P.O., Mazgaon, Mumbai 400 010 (IN).

(74) Agents: **WAIN, Christopher, Paul et al.**; A. A. Thornton & Co, 235 High Holborn, London WC1V 7LE (GB).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, 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, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

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 03/105856 A1

(54) Title: COMBINATION OF AZELASTINE AND STEROIDS

(57) Abstract: A pharmaceutical product or formulation, which comprises azelastine or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, and a steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, preferably the product or formulation being in a form suitable for nasal or ocular administration.

COMBINATION OF AZELASTINE AND STEROIDS

The present invention relates to pharmaceutical products and formulations. More particularly the present invention relates to pharmaceutical products and formulations useful for preventing or minimising allergic reactions. More particularly, but not exclusively, the present invention relates to pharmaceutical products and formulations for nasal and ocular use.

Such allergic reactions commonly comprise the allergy-related and vasomotor-related symptoms and the rhinovirus-related symptoms.

It is known to use antihistamines in nasal sprays and eye drops to treat allergy-related conditions. Thus, for example, it is known to use the antihistamine azelastine (usually as the hydrochloride salt) as a nasal spray against seasonal or perennial allergic rhinitis, or as eye drops against seasonal and perennial allergic conjunctivitis.

It is also known to treat these conditions using a corticosteroid, which will suppress nasal and ocular inflammatory conditions. Among the corticosteroids known for nasal use are, for example, beclomethasone, mometasone, fluticasone, budesonide and cyclosenide. Corticosteroids known for ocular anti-inflammatory use include betamethasone sodium, dexamethasone sodium and prednisolone acetate, for example.

It would be highly desirable, however, to provide a treatment that combines the effects of anti-histamine treatments and steroid treatments, in a pharmaceutically acceptable formulation, which is tolerated in situ, without significantly disrupting the potency of the constituent pharmaceuticals.

We have now found that, very surprisingly, azelastine (4-[(4-Chlorophenyl)methyl]-2-(hexahydro-1-methyl-1H-azepin-4-yl)-1(2H)-phthalazinone), or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, preferably in salt form and even more preferably in the form of the hydrochloride salt, can advantageously be combined with a steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, to provide a stable, very effective combination product or formulation preferably for nasal or ocular treatment. The combination can provide, in a single administration or dosing regime, the antihistaminic properties of azelastine and the anti-

inflammatory (and / or other) properties of the steroid, without any significant interference between the two, or adverse reaction in situ.

In one aspect the invention provides a pharmaceutical formulation comprising azelastine or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, and a steroid, preferably a corticosteroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, the formulation preferably being in a form suitable for administration nasally or ocularly.

The term "physiologically functional derivative" as used herein denotes a chemical derivative of any of the specific therapeutic agents described herein having the same or similar physiological function as the free base therapeutic agent and, for example, being convertible in the body thereto. According to the present invention, examples of physiologically functional derivatives include esters.

The preferred forms of formulations of the invention are nasal drops, eye drops, nasal sprays, nasal inhalation solutions or aerosols or insufflation powders.

Preferred embodiments of the invention can comprise stable aqueous solutions of azelastine or one or more of its salts, in combination with steroids which may be beclomethasone, mometasone, fluticasone, budesonide or cyclosenide, which can be used in the form of inhalation solution, pressurized aerosol, eye drops or nasal drops, and in a particular preferred embodiment, in the form of a spray (preferably a nasal spray). The spray can, for example, be formed by the use of a conventional spray-squeeze bottle or a pump vaporizer. In addition, it is also possible to use compressed gas aerosols. In a preferred embodiment, 0.03 to 3 mg of azelastine base and 0.05 to 0.15 mg of the steroid should be released per individual actuation.

The formulations preferably contain a preservative and/or stabilizer. These include, for example: ethylene diamine tetra-acetic acid (edetic acid) and its alkali salts (for example dialkali salts such as disodium salt, calcium salt, calcium-sodium salt), lower alkyl p-hydroxybenzoates, chlorhexidine (for example in the form of the acetate or gluconate) and phenyl mercury borate. Other suitable preservatives are: pharmaceutically useful quaternary ammonium compounds, for example cetylpyridinium chloride, tetradecyltrimethyl ammonium bromide, generally known as "cetrimide", benzyldimethyl-[2-[2-[p-(1,1,3,3-tetramethyl-butyl)phenoxy]ethoxy]-ammonium chloride, generally known as "benzethonium chloride" and myristyl picolinium chloride. Each of these compounds may be used in a

concentration of 0.002 to 0.05%, for example 0.02% (weight/volume in liquid formulations, otherwise weight/weight). Preferred preservatives among the quaternary ammonium compounds are, however, alkylbenzyl dimethyl ammonium chloride and mixtures thereof, for example the compounds generally known as "benzalkonium chloride".

The total amount of preservatives in the formulations (solutions, ointments, etc.) is preferably from 0.001 to 0.10g, preferably 0.01g per 100ml of solution/suspension or 100g of formulation.

In the case of preservatives, the following amounts of individual substances can, for example, be used: thimero sal 0.002-0.02%; benzalkonium chloride 0.002 to 0.02% (in combination with thimero sal the amount of thimero sal is, for example =0.002 to 0.005%;); chlorhexidine acetate or gluconate 0.01 to 0.02%; phenyl mercuric/nitrate, borate, acetate 0.002-0.004%; p-hydroxybenzoic acid ester (for example, a mixture of the methyl ester and propyl ester in the ratio 7:3): preferably 0.05-0.15, more preferably 0.1%.

The preservative used is preferably a combination of edetic acid (for example, as the disodium salt) and benzalkonium chloride. In this combination, the edetic acid is preferably used in a concentration of 0.05 to 0.1%, benzalkonium chloride preferably being used in a concentration of 0.005 to 0.05%, more preferably 0.01%.

In the case of solutions/suspensions reference is always made to percent by weight/volume, in the case of solid or semi-solid formulations to percent by weight/weight of the formulation.

Further auxiliary substances which may, for example, be used for the formulations of the invention are: polyvinyl pyrrolidone, sorbitan fatty acid esters such as sorbitan trioleate, polyethoxylated sorbitan fatty acid esters (for example polyethoxylated sorbitan trioleate), sorbimacrogol oleate, synthetic amphotensides (tritons), ethylene oxide ethers of octylphenolformaldehyde condensation products, phosphatides such as lecithin, polyethoxylated fats, polyethoxylated oleotriglycerides and polyethoxylated fatty alcohols. In this context, polyethoxylated means that the relevant substances contain polyoxyethylene chains, the degree of polymerisation of which is generally between 2 to 40, in particular between 10 to 20. These substances are preferably used to improve the solubility of the azelastine component.

It is optionally possible to use additional isotonization agents. Isotonization agents which may, for example, be used are: saccharose, glucose, glycerine, sorbitol, 1,2-propylene

glycol and NaCl.

The isotonization agents adjust the osmotic pressure of the formulations to the same osmotic pressure as nasal secretion. For this purpose these substances are in each case to be used in such amount that, for example, in the case of a solution, a reduction in the freezing point of 0.50 to 0.56 degree C is attained in comparison to pure water.

In Example 1, it is possible to use instead of NaCl per 100 ml of solution, for example: Glucose $1H_2O$ 3.81g; saccharose 6.35g; glycerine 2.2g; 1,2-propylene glycol 1.617g; sorbitol 3.84g (in the case of mixtures of these substances correspondingly less may optionally be used).

Moreover, it is possible to add thickening agents to solutions according to the present invention to prevent the solution from flowing out of the nose too quickly and to give the solution a viscosity of about 1.5 to 3, preferably 2 mPa.

Such thickening agents may, for example, be: cellulose derivatives (for example cellulose ether) in which the cellulose-hydroxy groups are partially etherified with lower unsaturated aliphatic alcohols and/or lower unsaturated aliphatic oxyalcohols (for example methyl cellulose, carboxymethyl cellulose, hydroxypropylmethylcellulose), gelatin, polyvinylpyrrolidone, tragacanth, ethoxose (water soluble binding and thickening agents on the basis of ethyl cellulose), alginic acid, polyvinyl alcohol, polyacrylic acid, pectin and equivalent agents. Should these substances contain acid groups, the corresponding physiologically acceptable salts may also be used.

In the event of the use of hydroxypropyl cellulose, 0.1% by weight of the formulation, for example, is used for this purpose.

In the event of the use of Avicel RC 591 or CLll, 0.65-3.0% by weight of the formulation, for example, is used for the purpose.

It is also possible to add to the formulations buffer substances such as citric acid/sodium hydrogensulphate borate buffer, phosphates (sodium hydrogenorthophosphate, disodium hydrogenphosphate), trometamol or equivalent conventional buffers in order, for example, to adjust the formulations to a pH value of 3 to 7, preferably 4.5 to 6.5.

The amount of citric acid is, for example, 0.01 to 0.14g, preferably 0.04 to 0.05g, the amount of disodium hydrogenphosphate 0.1 to 0.5g, preferably 0.2 to 0.3g per 100 ml of solution. The weights given relate in each case to the anhydrous substances.

In the case of solutions and suspensions, the maximum total concentration of active agent and buffer is preferably less than 5%, in particular less than 2% (weight/volume).

For the nasal application, a solution or suspension can preferably be used which is applied as an aerosol, i.e. in the form of a fine dispersion in air or in another conventional carrier gas, for example by means of a conventional pump vaporizer.

Application as a dosage aerosol is, however, also possible. Dosage aerosols are defined as being pressure packings which contain the azelastine or its salts in combination with steroid, in the form of a solution or suspension in a so-called propellant. The propellant may be a pressurized liquid chlorinated, fluorinated hydrocarbon or mixtures of various chlorinated, fluorinated hydrocarbons as well as propane, butane, isobutene or mixtures of these among themselves or with chlorinated, fluorinated hydrocarbons which are gaseous at atmospheric pressure and room temperature. Hydrofluorocarbons (HFCs), such as HFC 134a, and HFC 227a can also be used, and are preferred for environmental reasons. The pressure packing has a dosage or metering valve which, on actuation, releases a defined amount of the solution or suspension of the medicament. The subsequent very sudden vaporization of the propellant tears the solution or suspension of azelastine into the finest droplets or minute particles which can be sprayed in the nose or which are available for inspiration into the nose. Certain plastic applicators may be used to actuate the valve and to convey the sprayed suspension into the nose.

In the case of application as an aerosol, it is also possible to use a conventional adapter.

Particularly preferred embodiments of the present invention are hereinafter described and it will of course be appreciated that any of the previous description of suitable ingredients and formulation characteristics can also be applicable to the following products and formulations as provided by the present invention.

It will be appreciated, therefore, that the present invention further provides a pharmaceutical product comprising (i) azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, provided in an aerosol formulation preferably together with a propellant typically suitable for MDI delivery, and (ii) at least one steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, provided in an aerosol formulation preferably together with a propellant typically suitable for MDI delivery, as a combined preparation for simultaneous, separate or sequential

use in the treatment of conditions for which administration of one or more anti-histamine and / or one or more steroid is indicated.

The present invention also provides an aerosol formulation preferably suitable for MDI delivery comprising (i) azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, and (ii) at least one steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, together with a propellant.

It will also be appreciated from the above, that the respective therapeutic agents of the combined preparation can be administered simultaneously, either in the same or different pharmaceutical formulations, or separately or sequentially. If there is separate or sequential administration, it will also be appreciated that the subsequently administered therapeutic agents should be administered to a patient within a time scale so as to achieve, or more particularly optimise, the above referred to advantageous synergistic therapeutic effect of a combined preparation as present in a pharmaceutical product according to the present invention.

Suitable propellants for use in pharmaceutical products of formulations as provided by the present invention include 1,1,1,2-tetrafluoroethane (HFA 134a) or 1,1,1,2,3,3,3,-heptafluoropropane (HFA 227), or a combination of both, or mono-fluoro trichloromethane and dichloro difluoromethane, in particular 1,1,1,2-tetrafluoroethane (HFA 134a) or 1,1,1,2,3,3,3-heptafluoropropane (HFA 227), with HFA 134a being preferred.

A pharmaceutical aerosol formulation according to the present invention preferably further comprises a polar cosolvent such as C_{2-6} aliphatic alcohols and polyols, for example ethanol, isopropanol and propylene glycol, with ethanol often being preferred. Preferably, the concentration of the cosolvent is in the range of about 2 to 10% by weight, typically up to about 5%, of the total formulation.

A pharmaceutical aerosol formulation according to the present invention may further comprise one or more surfactants. Such surfactants can be included to stabilise the formulations and for lubrication of a valve system. Some of the most commonly used surfactants in aerosol formulations are oils derived from natural sources, such as corn oil, olive oil, cottonseed oil and sunflower seed oil, and also phospholipids. Suitable surfactants can include lecithin, oleic acid or sorbitan oleate.

A further preferred embodiment of the present invention can be where a formulation

or product is provided in the form of insufflatable powder, where preferably the maximum particle size of the substance suitably does not exceed 10μm. Azelastine or its salts and the steroid may be mixed with inert carrier substances or drawn up onto inert carrier substances. Carrier substances which may, for example, be used are: sugars such as glucose, saccharose, lactose and fructose. Also starches or starch derivatives, oligosaccharides such as dextrins, cyclodextrins and their derivatives, polyvinylpyrrolidone, alginic acid, tylose, silicic acid, cellulose, cellulose derivatives (for example cellulose ether), sugar alcohols such as mannitol or sorbitol, calcium carbonate, calcium phosphate, etc.

In one embodiment, the therapeutic agents employed have a particle size of less than about 10 μm, preferably less than 5 μm.

The use of insufflation powders can represent a preferred embodiment of the present invention and there is provided by the present invention a pharmaceutical product comprising (i) azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, provided as an insufflation powder, and (ii) at least one steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, provided as an insufflation powder, as a combined preparation for simultaneous, separate or sequential use in the treatment of conditions for which administration of one or more anti-histamine and / or one or more steroid is indicated.

It will be appreciated from the above, that the respective therapeutic agents of the combined preparation can be administered simultaneously, either in the same or different insufflation powder formulations, or separately or sequentially. If there is separate or sequential administration as discussed above, it will also be appreciated that the subsequently administered therapeutic agents should be administered to a patient within a time scale so as to achieve, or more particularly optimise, the above referred to advantageous synergistic therapeutic effect of a combined preparation as present in a pharmaceutical product according to the present invention.

The present invention also provides an insufflation powder formulation comprising (i) azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, and (ii) at least one steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, together with a pharmaceutically acceptable carrier or excipient therefor.

Dry insufflation powder formulations as provided by the present invention can be

beneficial where it is required that therapeutic agents as employed according to the present invention are retained in the nasal cavity, and systemic side effects can be minimised or eliminated. Furthermore, insufflation powder formulations as employed in the present invention can be beneficial whereby retention of azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, at the nasal mucosa is improved, and the bitter aftertaste associated with liquid antihistamine formulations significantly reduced, whilst also exhibiting the synergistic therapeutic effect associated with the azelastine / steroid combinations provided by the present invention. By providing a dry insufflation powder formulation of azelastine, together with a steroid, having an average particle size of less than about 10 μm, the therapeutic agents can be restricted primarily to the desired target organ, the nasal mucosa.

A dry powder insufflation formulation according to the present invention can be administered by the use of an insufflator, which can produce a finely divided cloud of the dry powder. The insufflator preferably is provided with means to ensure administration of a substantially pre-determined amount of a formulation or product as provided by the present invention. The powder may be used directly with an insufflator which is provided with a bottle or container for the powder, or the powder may be filled into a capsule or cartridge, such as a gelatin capsule, or other single dose device adapted for administration. The insufflator preferably has means to open the capsule or other dose device.

Preferred combinations of therapeutic agents employed in pharmaceutical products and formulations according to the present invention (in particular nasal sprays or drops, aerosol or insufflation products and formulations as described above) comprise any one of the following combinations.

The present invention further provides, therefore, a pharmaceutical product comprising (i) azelastine, or a pharmaceutically acceptable salt thereof, and (ii) at least one steroid selected from the group consisting of beclomethasone, fluticasone, mometasone and pharmaceutically acceptable esters thereof, as a combined preparation for simultaneous, separate or sequential use in the treatment of conditions for which administration of one or more anti-histamine and / or one or more steroid is indicated. Suitably the esters can be selected from beclomethasone dipropionate, fluticasone propionate, fluticasone valerate, mometasone furoate and mometasone furoate monohydrate.

The present invention also provides a pharmaceutical formulation comprising (i) azelastine, or a pharmaceutically acceptable salt thereof, and (ii) at least one steroid selected from the group consisting of beclomethasone, fluticasone, mometasone and pharmaceutically acceptable esters thereof, together with a pharmaceutically acceptable carrier or excipient therefor. Suitably the esters can be selected from beclomethasone dipropionate, fluticasone propionate, fluticasone valerate, mometasone furoate and mometasone furoate monohydrate.

In the case of a nasal spray, a particularly preferred formulation as provided by the present invention is a nasal spray comprising azelastine, or a pharmaceutically acceptable salt thereof (preferably azelastine hydrochloride), together with mometasone either as the free base or in ester form, preferably as mometasone furoate.

Specific combinations of therapeutic agents employed in pharmaceutical products and formulations according to the present invention comprise any one of the following combinations:

azelastine hydrochloride and beclomethasone dipropionate;

azelastine hydrochloride and fluticasone propionate;

azelastine hydrochloride and fluticasone valerate;

azelastine hydrochloride and mometasone furoate; and

azelastine hydrochloride and mometasone furoate monohydrate.

There is also provided by the present invention a method for the prophylaxis or treatment in a mammal, such as a human, of conditions for which administration of one or more anti-histamine and / or one or more steroid is indicated, which method comprises administration of a therapeutically effective amount of a pharmaceutical product substantially as hereinbefore described, as a combined preparation for simultaneous, separate or sequential use in the treatment of such conditions.

The present invention also provides a method for the prophylaxis or treatment in a mammal, such as a human, of conditions for which administration of one or more anti-histamine and / or one or more steroid is indicated, which method comprises administration of a therapeutically effective amount of a pharmaceutical formulation substantially as hereinbefore described.

There is also provided by the present invention for use in the manufacture of a medicament for the prophylaxis or treatment in a mammal, such as a human, of conditions for which administration of one or more anti-histamine and / or one or more steroid is indicated,

a pharmaceutical product, as a combined preparation for simultaneous, separate or sequential use in the treatment of such conditions.

There is further provided by the present invention, therefore, a process of preparing a pharmaceutical product substantially as hereinbefore described, which process comprises providing as a combined preparation for simultaneous, separate or sequential use in the treatment of conditions for which administration of one or more anti-histamine and / or one or more steroid is indicated: (i) azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, and (ii) at least one steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.

The present invention also provides a process of preparing a pharmaceutical formulation substantially as hereinbefore described, which process comprises admixing a pharmaceutically acceptable carrier or excipient with: (i) azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, and (ii) at least one steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof. Preferably pharmaceutical formulations according to the present invention can comprise insufflation powder formulations, nasal sprays, nasal inhalation solutions or aerosols substantially as hereinbefore described.

The present invention is now illustrated by the following Examples, which do not limit the scope of the invention in any way. In Examples where only the ingredients of formulations according to the present invention are listed, these formulations are prepared by techniques well known in the art.

Example 1

Nasal spray or nasal drops with 0.1% azelastine hydrochloride as active ingredient and steroid 0.1%

Sr. No	Ingredients	Quantity %w/v
1.	Azelastine hydrochloride	0.1%
2.	Steroid	0.1%
3.	Disodium edetate	0.005%

4.	Sodium chloride	0.9%
5.	Benzalkonium chloride	0.001%
6.	Avicel RC 591	1.2%
7.	Citric acid monohydrate	0.2%
8.	Disodium hydrogen phosphate dodecahydrate	0.1%
9.	Purified water	

Example 2

Dosage aerosol giving off 0.5 mg of azelastine hydrochloride and 50 micrograms of beclomethasone dipropionate freon solvate per stroke.

About 8.0 kg of a mixture of 70 parts by weight of difluorodichloromethane and 30 parts by weight of 1,2dichlorotetrafluoroethane are cooled to about -55 degree C in an appropriate cooling vessel. A mixture of 0.086 kg of pre-cooled sorbitantrioleate and 0.8600 kg of pre-cooled trichlorofluoromethane are dissolved with stirring into the mixture at -55 degrees C, 0.0688 kg of micronized azelastine hydrochloride, 0.00688 kg of beclomethasone dipropionate freon solvate and 0.0688 kg of micronized lactose are then incorporated in portions into the solution thereby obtained with intensive stirring. The total weight of the suspension thereby obtained is made up to 9.547 kg through addition of more of the mixture of 70 parts by weight of difluorodichloromethane and 30 parts by weight of 1,2-dichlorotetrafluoroethane cooled to about -55 degree C.

Following closure of the cooling vessel the suspension is again cooled to about -55 degrees C under intensive stirring. It is then ready to be filled.

Example 3

Nasal spray or nasal drops with Azelastine and steroid*

Sr. No.	Ingredients	Quantity (% w/w)
	Azelastine Hydrochloride	0.10

	Fluticasone propionate	0.0357
	Glycerin	2.60
	Avicel RC 591	1.35
	Polysorbate 80	0.025
	Benzalkonium chloride	0.01
	Phenyl ethyl alcohol	0.25
	Purified water	q. s.

*Each spray delivers Azelastine Hydrochloride (140 mcg) and Fluticasone propionate (50 mcg).

Example 4

Nasal spray or nasal drops with Azelastine and steroid*

Sr. No.	Ingredients	Quantity (% w/w)
	Azelastine Hydrochloride	0.10
	Fluticasone valerate	0.0357
	Glycerin	2.60
	Avicel RC 591	1.20
	Polysorbate 80	0.030
	Benzalkonium chloride	0.01
	Phenyl ethyl alcohol	0.25
	Purified water	q. s.

*Each spray delivers Azelastine Hydrochloride (140 mcg) and Fluticasone valerate (50 mcg).

Example 5

Nasal spray or nasal drops with Azelastine and steroid*

Sr. No.	Ingredients	Quantity (% w/w)
	Azelastine Hydrochloride	0.10
	Fluticasone propionate	0.0714
	Glycerin	2.60
	Avicel RC 581	1.35
	Polysorbate 80	0.025
	Benzalkonium chloride	0.01
	Phenyl ethyl alcohol	0.25
	Purified water	q. s.

*Each spray delivers Azelastine Hydrochloride (140 mcg) and Fluticasone propionate (50 mcg).

Example 6

Nasal spray or nasal drops with Azelastine and steroid

Sr. No.	Ingredients	Quantity (% w/w)
	Azelastine Hydrochloride	0.10
	Mometasone Furoate	0.05173
	Glycerin	2.30
	Disodium edetate	0.005
	Polysorbate 80	0.0125
	Avicel RC 581	1.35
	Benzalkonium chloride	0.01
	Citric acid monohydrate	0.20
	Disodium hydrogen phosphate	0.10

	dodecahydrate	
	Purified water	q. s.

Example 7

Nasal spray or nasal drops with Azelastine and steroid*

Sr. No.	Ingredients	Quantity (% w/w)
	Azelastine Hydrochloride	0.10
	Mometasone Furoate monohydrate	0.05173
	Glycerin	2.60
	Avicel CL 611	2.295
	Polysorbate 80	0.0125
	Benzalkonium chloride	0.01
	Phenyl ethyl alcohol	0.25
	Purified water	q. s.

*Each spray delivers Azelastine Hydrochloride (140 mcg) and Mometasone furoate (50 mcg).

Example 8

Nasal MDI with Azelastine and steroid

Sr. No.	Ingredients	Quantity in mcg
	Azelastine Hydrochloride	140
	Mometasone Furoate monohydrate	50
	HFA 134a	q.s.
	Lecithin	0.1%
	Alcohol	(up to 5%)

Example 9

Nasal MDI with Azelastine and steroid

Sr. No.	Ingredients	Quantity in mcg
	Azelastine Hydrochloride	140
	Fluticasone propionate	50
	HFA 134a	q.s.
	Sorbitan trioleate	0.1%
	Alcohol	(up to 5%)

Example 10

Nasal MDI with Azelastine and steroid

Sr. No.	Ingredients	Quantity in mcg
	Azelastine Hydrochloride	140
	Fluticasone propionate	100
	HFA 134a	q.s.
	Oleic acid	0.1%

Example 11

Nasal MDI with Azelastine and steroid

Sr. No.	Ingredients	Quantity in mcg
	Azelastine Hydrochloride	140
	Fluticasone Valerate	50
	HFA 134a	q.s.
	Alcohol	(up to 5%)

Insufflatable powders containing Azelastine and Steroid:

Example 12

Sr. No.	Ingredients	Quantity (% w/w)
	Azelastine Hydrochloride (Micronized)	140 mcg
	Fluticasone propionate	50 mcg
	Lactose	q.s. (up to 25 mcg)

Example 13

Sr. No.	Ingredients	Quantity (% w/w)
	Azelastine Hydrochloride (Micronized)	140 mcg
	Fluticasone propionate	100 mcg
	Mannitol	q.s. (up to 30 mcg)

Example 14

Sr. No.	Ingredients	Quantity (% w/w)
	Azelastine Hydrochloride (Micronized)	140 mcg
	Fluticasone propionate	250 mcg
	Lactose	q.s. (up to 30 mcg)

CLAIMS:

1 A pharmaceutical formulation which comprises azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, and a steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, preferably the formulation being in a form suitable for nasal or ocular administration.

2 A pharmaceutical formulation according to claim 1, wherein said azelastine is present as azelastine hydrochloride.

3 A formulation according to claim 1 or 2, wherein the steroid is beclomethasone or a pharmaceutically acceptable ester thereof, mometasone or a pharmaceutically acceptable ester thereof, fluticasone or a pharmaceutically acceptable ester thereof, budesonide or cyclosenide, in any chiral form or mixture.

4 A formulation according to claim 3, wherein the steroid is beclomethasone propionate, mometasone furoate, mometasone furoate monohydrate, fluticasone propionate or fluticasone valerate.

5 A formulation according to any of claims 1 to 4, which contains the steroid in an amount from about 50 micrograms/ml to about 5 mg/ml of the formulation.

6 A formulation according to any of claims 1 to 5, wherein the formulation has a particle size of less than about 10 μm, preferably less than 5 μm.

7 A formulation according to any of claims 1 to 6, which is a suspension containing 0.0005 to 2% (weight/weight of the formulation) of azelastine or a pharmaceutically acceptable salt of azelastine, and from 0.5 to 1.5% (weight/weight of the formulation) of said steroid.

8 A formulation according to claim 7, which contains from 0.001 to 1% (weight/weight of the formulation) azelastine, or salt thereof, and from 0.5% to 1.5% (weight/weight of the

formulation) steroid.

9 A formulation according to any of claims 1 to 8, which also contains a surfactant.

10 A formulation according to claim 9, wherein the surfactant comprises a polysorbate or poloxamer surfactant.

11 A formulation according to claim 9 or 10, which contains from about 50 micrograms to about 1 milligram of surfactant per ml of the formulation.

12 A formulation according to any of claims 1 to 11, which also contains an isotonic agent.

13 A formulation according to claim 12, wherein the isotonic agent comprises sodium chloride, saccharose, glucose, glycerine, sorbitol or 1,2-propylene glycol.

14 A formulation according to any of claims 1 to 13, which also contains at least one of a buffer, a preservative and a suspending or thickening agent.

15 A formulation according to claim 14, wherein said preservative is selected from edetic acid and its alkali salts, lower alkyl p-hydroxybenzoates, chlorhexidine, phenyl mercury borate, or benzoic acid or a salt, a quaternary ammonium compound, or sorbic acid or a salt thereof.

16 A formulation according to claim 14 or 15, wherein the suspending agent or thickening agent is selected from cellulose derivatives, gelatin, polyvinylpyrrolidone, tragacanth, ethoxose (water soluble binding and thickening agents on the basis of ethyl cellulose), alginic acid, polyvinyl alcohol, polyacrylic acid, or pectin.

17 A formulation according to any of claims 14, 15 or 16, wherein the buffer comprises a citric acid-citrate buffer.

18 A formulation according to any of claims 14, 15, 16 or 17, wherein the buffer maintains the pH of the aqueous phase at from 3 to 7, preferably 4.5 to about 6.5.

19 A formulation according to any of claims 1 to 18, which is an aqueous suspension or solution.

20 A formulation according to claim 19, which is in the form of an aerosol, an ointment, eye drops, nasal drops, a nasal spray or an inhalation solution.

21 A formulation according to claim 20, which is in the form of nasal drops or nasal spray.

22 A formulation according to claim 20, which is in the form of an aerosol.

23 A pressure packing having a dosage or metering valve, which contains a formulation according to claim 22.

24 A MDI which includes a pressure packing according to claim 23.

25 A formulation according to any of claims 1 to 19, which is in the form of an insufflation powder.

26 A pharmaceutical product comprising (i) azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, provided in an aerosol formulation preferably together with a propellant typically suitable for MDI delivery, and (ii) at least one steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, provided in an aerosol formulation preferably together with a propellant typically suitable for MDI delivery, as a combined preparation for simultaneous, separate or sequential use in the treatment of conditions for which administration of one or more anti-histamine and / or one or more steroid is indicated.

27 An aerosol formulation preferably suitable for MDI delivery comprising (i) azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, and (ii) at least one steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, together with a propellant.

28 A pharmaceutical product comprising (i) azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, provided as an insufflation powder, and (ii) at least one steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, provided as an insufflation powder, as a combined preparation for simultaneous, separate or sequential use in the treatment of conditions for which administration of one or more anti-histamine and / or one or more steroid is indicated.

29 An insufflation powder formulation comprising (i) azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, and (ii) at least one steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, together with a pharmaceutically acceptable carrier or excipient therefor.

30 A pharmaceutical product comprising (i) azelastine, or a pharmaceutically acceptable salt thereof, and (ii) at least one steroid selected from the group consisting of beclomethasone, fluticasone, mometasone and pharmaceutically acceptable esters thereof, as a combined preparation for simultaneous, separate or sequential use in the treatment of conditions for which administration of one or more anti-histamine and / or one or more steroid is indicated.

31 A pharmaceutical formulation comprising (i) azelastine, or a pharmaceutically acceptable salt thereof, and (ii) at least one steroid selected from the group consisting of beclomethasone, fluticasone, mometasone and pharmaceutically acceptable esters thereof, together with a pharmaceutically acceptable carrier or excipient therefor.

32 A nasal spray comprising azelastine, or a pharmaceutically acceptable salt thereof, together with mometasone either as mometasone free base or as mometasone furoate, and a pharmaceutically acceptable carrier or excipient therefor.

33 A pharmaceutical product comprising azelastine hydrochloride and beclomethasone dipropionate, as a combined preparation for simultaneous, separate or sequential use in the treatment of conditions for which administration of one or more anti-histamine and / or one or more steroid is indicated.

34 A pharmaceutical formulation comprising azelastine hydrochloride and beclomethasone dipropionate, together with a pharmaceutically acceptable carrier or excipient therefor.

35 A pharmaceutical product comprising azelastine hydrochloride and fluticasone propionate, as a combined preparation for simultaneous, separate or sequential use in the treatment of conditions for which administration of one or more anti-histamine and / or one or more steroid is indicated.

36 A pharmaceutical formulation comprising azelastine hydrochloride and fluticasone propionate, together with a pharmaceutically acceptable carrier or excipient therefor.

37 A pharmaceutical product comprising azelastine hydrochloride and fluticasone valerate, as a combined preparation for simultaneous, separate or sequential use in the treatment of conditions for which administration of one or more anti-histamine and / or one or more steroid is indicated.

38 A pharmaceutical formulation comprising azelastine hydrochloride and fluticasone valerate, together with a pharmaceutically acceptable carrier or excipient therefor.

39 A pharmaceutical product comprising azelastine hydrochloride and mometasone furoate, as a combined preparation for simultaneous, separate or sequential use in the

treatment of conditions for which administration of one or more anti-histamine and / or one or more steroid is indicated.

40 A pharmaceutical formulation comprising azelastine hydrochloride and mometasone furoate, together with a pharmaceutically acceptable carrier or excipient therefor.

41 A pharmaceutical product comprising azelastine hydrochloride and mometasone furoate monohydrate, as a combined preparation for simultaneous, separate or sequential use in the treatment of conditions for which administration of one or more anti-histamine and / or one or more steroid is indicated.

42 A pharmaceutical formulation comprising azelastine hydrochloride and mometasone furoate monohydrate, together with a pharmaceutically acceptable carrier or excipient therefor.

43 A pharmaceutical formulation substantially as herein described in any of the Examples.

44 A process of preparing a pharmaceutical product according to any of claims 26, 28, 30, 33, 35, 37, 39 or 41, which process comprises providing (i) azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, and (ii) at least one steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, as a combined preparation for simultaneous, separate or sequential use in the treatment of conditions for which administration of one or more anti-histamine and / or one or more steroid is indicated.

45 A process of preparing a pharmaceutical formulation according to any of claims 1 to 22, 27, 29, 31, 32, 34, 36, 38, 40, 42 or 43, which process comprises admixing a pharmaceutically acceptable carrier or excipient with azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, and at least one steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof.

46 A method for the prophylaxis or treatment in a mammal, such as a human, of conditions for which administration of one or more anti-histamine and / or one or more steroid is indicated, which method comprises administration of a therapeutically effective amount of a pharmaceutical product according to any of claims 26, 28, 30, 33, 35, 37, 39 or 41, as a combined preparation for simultaneous, separate or sequential use in the treatment of such conditions.

47 A method for the prophylaxis or treatment in a mammal, such as a human, of conditions for which administration of one or more anti-histamine and / or one or more steroid is indicated, which method comprises administration of a therapeutically effective amount of a pharmaceutical formulation according to any of claims 1 to 22, 27, 29, 31, 32, 34, 36, 38, 40, 42 or 43.

48 For use in the manufacture of a medicament for the prophylaxis or treatment in a mammal, such as a human, of conditions for which administration of one or more anti-histamine and / or one or more steroid is indicated, a pharmaceutical product according to any of claims 26, 28, 30, 33, 35, 37, 39 or 41, as a combined preparation for simultaneous, separate or sequential use in the treatment of such conditions.

49 A method of treating irritation or disorders of the nose or eye which comprises applying either directly to nasal tissues or to the conjunctival sac of the eyes, as appropriate, a pharmaceutical product according to any of claims 26, 28, 30, 33, 35, 37, 39 or 41, or a pharmaceutical formulation according to any of claims 1 to 22, 27, 29, 31, 32, 34, 36, 38, 40, 42 or 43.

50 A method of treating airway disorders, comprising administering by nebulization to surfaces of the airway a treatment-effective amount of a product or formulation as defined in the preceding claims.

INTERNATIONAL SEARCH REPORT

Internal application No
PCT/GB 03/02557

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/55 A61K31/56 A61K31/57 A61K31/58 A61K9/00
A61P37/08 A61P27/14 A61P11/06 //(A61K31/56,31:55),
(A61K31/57,31:55),(A61K31/58,31:55)

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 A61P

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)
EPO-Internal, MEDLINE, WPI Data, PAJ, BIOSIS, EMBASE, 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	WO 97 01337 A (MCNEIL PPC INC) 16 January 1997 (1997-01-16) page 2, line 8 -page 8, line 25 ---	1-50
X	EP 0 780 127 A (PROCTER & GAMBLE) 25 June 1997 (1997-06-25) page 2, line 34 -page 5, line 30; example 3 --- -/--	1-50

[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
1 September 2003	17/09/2003

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	Vandenbogaerde, A

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

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE MEDLINE 'Online! US NATIONAL LIBRARY OF MEDICINE (NLM), BETHESDA, MD, US; 2000 PORTMANN D ET AL: "'Acceptability of local treatment of allergic rhinitis with a combination of a corticoid (beclomethasone) and an antihistaminic (azelastine)!" Database accession no. NLM11233712 XP002252974 abstract & REVUE DE LARYNGOLOGIE - OTOLOGIE - RHINOLOGIE. FRANCE 2000, vol. 121, no. 4, 2000, pages 273-279, ISSN: 0035-1334	1-50
X	BUSSE W W ET AL: "CORTICOSTEROID-SPARING EFFECT OF AZELASTINE IN THE MANAGEMENT OF BRONCHIAL ASTHMA" AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE, AMERICAN LUNG ASSOCIATION, NEW YORK, NY, US, vol. 153, no. 1, 1996, pages 122-127, XP000604179 ISSN: 1073-449X page 127, column 1, paragraph 2	1-50

INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/GB 03/02557

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9701337 A	16-01-1997	AU 6392496 A	30-01-1997
		WO 9701337 A1	16-01-1997
EP 0780127 A	25-06-1997	EP 0780127 A1	25-06-1997

PATENT APPLICATION FEE DETERMINATION RECORD

Effective December 8, 2004

Application or Docket Number: 10/518016

CLAIMS AS FILED - PART I

SMALL ENTITY TYPE ☐ OR OTHER THAN SMALL ENTITY

	(Column 1)	(Column 2)	SMALL ENTITY RATE	SMALL ENTITY FEE		OTHER THAN SMALL ENTITY RATE	OTHER THAN SMALL ENTITY FEE
U.S. NATIONAL STAGE FEES							
BASIC FEE	SMALL ENT. = $ 150	LARGE ENT. = $ 300	BASIC FEE		OR	BASIC FEE	300
EXAMINATION FEE	Satisfies PCT Article 33(1)-(4) = $ 50 / $ 100	All other situations = $ 100 / $ 200	EXAM FEE			EXAM FEE	200
SEARCH FEE	U.S. is ISA = $ 50 / $ 100 ALL other countries = $ 200 / $ 400	All other situations = $ 250 / $ 500	SEARCH FEE			SEARCH FEE	400
FEE FOR EXTRA SPEC. PGS.	minus 100 =	/ 50 =	X $ 125 =			X $ 250 =	
TOTAL CHARGEABLE CLAIMS	51 minus 20 =	* 31	X $ 25 =		OR	X $ 50 =	1550
INDEPENDENT CLAIMS	3 minus 3 =	*	X $ 100 =		OR	X $ 200 =	
MULTIPLE DEPENDENT CLAIM PRESENT	☐		+ $ 180 =		OR	+ $ 360 =	
* If the difference in column 1 is less than zero, enter "0" in column 2			TOTAL		OR	TOTAL	1950

CLAIMS AS AMENDED - PART II

12-14-04

SMALL ENTITY OR OTHER THAN SMALL ENTITY

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE	SMALL ENTITY ADDITIONAL FEE		OTHER THAN SMALL ENTITY RATE	OTHER THAN SMALL ENTITY ADDITIONAL FEE
AMENDMENT A	Total	* 51	Minus	** 51	= 1	X $ 25 =		OR	X $ 50 =	
	Independent	* 3	Minus	*** 3	=	X $ 100 =		OR	X $ 200 =	
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM ☐					+ $ 180 =		OR	+ $ 360 =	
						TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

1, 28, 29

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE	SMALL ENTITY ADDITIONAL FEE		OTHER THAN SMALL ENTITY RATE	OTHER THAN SMALL ENTITY ADDITIONAL FEE
AMENDMENT B	Total	*	Minus	**	=	X $ 25 =		OR	X $ 50 =	
	Independent	*	Minus	***	=	X $ 100 =		OR	X $ 200 =	
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM ☐					+ $ 180 =		OR	+ $ 360 =	
						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.