UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 8,168,620 B2
APPLICATION NO. : 10/518016
DATED : May 1, 2012
INVENTOR(S) : Amar Lulla et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the claims:

Column 12, Claim 7, Line 7; Replace: "a suspending agent a thickening agent" with --a suspending agent, a thickening agent--
Column 12, Claim 10, Lines 20-21; Replace: "phenyl mercury borate, or benzoic acid" with --phenyl mercury borate, benzoic acid--
Column 13, Claim 24, Lines 19-20; Replace: "dosage form of as a nasal spray" with --dosage form of a nasal spray--

Signed and Sealed this
Eighteenth Day of November, 2014

Michelle K. Lee

Michelle K. Lee
Deputy Director of the United States Patent and Trademark Office

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patentees: Amar Lulla, *et al.*

Patent No.: 8,168,620 B2

Issued: May 1, 2012

For: COMBINATION OF AZELASTINE AND STEROIDS

§
§ Group Art Unit: 1616
§
§ Examiner: Thor B. Nielson
§
§ Confirmation No.: 4912
§
§

Mail Stop: Certificate of Correction Branch
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

CERTIFICATE OF FILING

Pursuant to 37 C.F.R. § 1.8, I hereby certify that this correspondence is being electronically submitted to the U.S. Patent and Trademark Office website, www.uspto.gov, on

9-18-2014

Adrianna Krenzer

PETITION FOR CERTIFICATE OF CORRECTION

Commissioner:

Patentees hereby request that a Certificate of Correction be issued pursuant to 37 C.F.R. §1.322 and 37 C.F.R. §1.323 to correct the mistakes as set out in the attached draft certificate.

The mistakes to be corrected are minor and editorial in nature. The Commissioner is hereby authorized to charge payment of any fees associated with submission of the Certificate of Correction submitted herewith to Deposit Account 50-1515, Conley Rose, P.C.

Respectfully submitted,

Date: 9-18-14

Rodney B. Carroll
Reg. No. 39,624

ATTORNEY FOR APPLICANTS

CONLEY ROSE, P.C.
5601 Granite Parkway, Suite 500
Plano, Texas 75024
(972) 731-2288
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PTO/SB/44 (08-07)
Approved for use through 08/31/2013. OMB 0651-0033
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

(Also Form PTO-1050)

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 8168620

APPLICATION NO.: 10518016

ISSUE DATE : May 1, 2012

INVENTOR(S) : Amar Lulla, Geena Malhotra

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the claims:

Column 12, Claim 7, Line 7; Replace: "a suspending agent a thickening agent" with --a suspending agent, a thickening agent--
Column 12, Claim 10, Lines 20-21; Replace: "phenyl mercury borate, or benzoic acid" with --phenyl mercury borate, benzoic acid--
Column 13, Claim 24, Lines 19-20; Replace: "dosage form of as a nasal spray" with --dosage form of a nasal spray--

MAILING ADDRESS OF SENDER (Please do not use customer number below):

Conley Rose, P.C., Rodney B. Carroll
5601 Granite Parkway, Suite 500
Plano, Texas 75024

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/Adrianna Krenzer
Attorney Docket Number:	CRT/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:				
Certificate of Correction	1811	1	100	100
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**100**

Electronic Acknowledgement Receipt

EFS ID:	20178591
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/Adrianna Krenzer
Filer Authorized By:	Rodney B. Carroll
Attorney Docket Number:	CRT/20632 US (4137-04700)
Receipt Date:	18-SEP-2014
Filing Date:	06-JUL-2005
Time Stamp:	16:11:19
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	$100
RAM confirmation Number	2699
Deposit Account	501515
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
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1	Request for Certificate of Correction	091814_RequestforCertofCorrection.pdf	112369 ce5f28c75770dc11575ed5dc97e5a2b819e712f1	no	2
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30131 c3768dc15928d5d29d2a317d523c53afce7cfa04	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	142500	

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New Applications Under 35 U.S.C. 111
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New International Application Filed with the USPTO as a Receiving Office
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United States Patent and Trademark Office
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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/518,016	05/01/2012	8168620	CRT/20632 US (4137-04700)	4912

30652 7590 04/11/2012

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

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

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

The Patent Term Adjustment is 987 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

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

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

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

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

Amar Lulla, Mumbai, INDIA;
Geena Malhotra, Mumbai, INDIA;

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	Thor B. Nielsen
	Attorney Docket Number	CRT/20632 US(4137-04700)

	9	4710495		1987-12-01	Bodor	
	10	5837699		1998-11-17	Sequeira, et al.	
	11	3755302		1973-08-28	Ercoli, et al.	
	12	3557162		1971-01-19	Voorschoten, et al.	
	13	5420120		1995-05-30	Boltralik	
	14	3828080		1974-08-06	May, et al.	
	15	5081113		1992-01-14	Claussner, et al.	
Change(s) applied to document. /J.L.B./ 3/28/2012	16	4861765		1989-08-29	Mitsukuchi et al. ~~Jouvoinal~~	
	17	4267173		1981-05-12	Draper	
	18	4221787		1980-09-09	Bodor, et al.	
	19	5608093		1997-03-04	Stache, et al.	

/Thor Nielsen/ 01/13/2012

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	Thor B. Nielsen
Attorney Docket Number	CRT/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	4198403		1980-04-15	Alvarez	
	2	6261539		2001-07-17	Adjei, et al.	
	3	4187301		1980-02-05	Edwards	
	4	5972920		1999-10-26	Seidel	
Change(s) applied to document, /J.L.B./ 3/28/2012	5	4377575		1983-03-22	Stache et al. ~~Phillipps, et al.~~	
	6	3856828		1974-12-24	Phillipps, et al.	
	7	4113680		1978-09-12	Kamano, et al.	
	8	4093721		1978-06-06	Phillipps, et al.	

/Thor Nielsen/ 01/13/2012

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	Thor B. Nielsen
	Attorney Docket Number	CRT/20632 US(4137-04700)

	46	0154481	WO		2001-08-02	Rohm and Haas Company		☐
	47	1191965	GB		1970-05-13	Warner-Lambert Pharmaceutical Company		☐
	48	0048587	WO		2000-08-24	Novartis AG, et al.		☐
Change(s) applied to document. /J.L.B./ 4/3/2012	49	0104118	WO		1/2001 ~~2011-01-18~~	Almirall Prodesfarma S.A.		☐
	50	0157025	WO		2001-08-09	Pfizer Products Inc.		☐

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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.	T5
	1	"Azelastine," STN Registry No. 58581-89-8, STN Registry File, Retrieved 2010-11-23, page 1.	☐
	2	"Fluticasone Furoate," STN Registry No. 397864-44-7, STN Registry File, Retrieved 2010-11-23, page 1.	☐
	~~3~~	Astelin (azelastine hydrochloride) Nasal Spray, MedPointe Pharmaceuticals, 2006, U.S. Physicians Desk Reference, pp. 1876-1877.	☐
	~~4~~	~~Veramyst (fluticasone furoate) Nasal Spray, GlaxoSmithKline, 2007, Summary Sheet, pp. 1-20.~~	☐

/Thor Nielsen/ 01/13/2012

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
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Certificate of Mailing or Transmission

I hereby certify that this correspondence is being electronically submitted to the U.S. Patent and Trademark Office website, "www.uspto.gov" [37 CFR 1.8 (a)].

Edith Shek	(Depositor's name)
Edith Shek	(Signature)
3/22/12	(Date)

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

TITLE OF INVENTION: COMBINATION OF AZELASTINE AND STEROIDS

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1740	$300	$0	$2040	04/30/2012

EXAMINER	ART UNIT	CLASS-SUBCLASS
NIELSEN, THOR B	1616	514-171000

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

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

1 Conley Rose, P.C.
2 Rodney B. Carroll
3

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

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

(A) NAME OF ASSIGNEE: CIPLA Limited

(B) RESIDENCE: (CITY and STATE OR COUNTRY): Mumbai, India

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

4a. The following fee(s) are submitted:
☑ Issue Fee
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5. **Change in Entity Status** (from status indicated above)
☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.
☐ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

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

Authorized Signature _____ Date 3-22-12

Typed or printed name Rodney B. Carroll Registration No. 39624

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

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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/Heather Franklin
Attorney Docket Number:	CRT/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:				
Utility Appl issue fee	1501	1	1740	1740
Publ. Fee- early, voluntary, or normal	1504	1	300	300

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**2040**

Electronic Acknowledgement Receipt

EFS ID:	12369945
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:	CRT/20632 US (4137-04700)
Receipt Date:	22-MAR-2012
Filing Date:	06-JUL-2005
Time Stamp:	16:29:36
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	$2040
RAM confirmation Number	3545
Deposit Account	501515
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
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1	Issue Fee Payment (PTO-85B)	032212_IssueFee.pdf	126851 2024bbd12590d60d9c7739561d2a6c9876719588	no	1
Warnings:					
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2	Fee Worksheet (SB06)	fee-info.pdf	32066 b8853580105c9a59c301daddd5356de4971c9a27	no	2
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New Applications Under 35 U.S.C. 111
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National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

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

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

30652 7590 03/20/2012

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EXAMINER	
NIELSEN, THOR B	

ART UNIT	PAPER NUMBER
1616	

MAIL DATE	DELIVERY MODE
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APPLICATION NO./ CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR / PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.
10/518,016	06 July, 2005	LULLA ET AL.	CRT/20632 US (4137-04700)

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EXAMINER	
THOR NIELSEN	
ART UNIT	PAPER
1616	20120315

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Commissioner for Patents

The references identified on the attached Information Disclosure Statement, filed on 02/23/2012, have been considered. TBN

/T. N./
Examiner, Art Unit 1616

PTO-90C (Rev.04-03)

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (01-10)
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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	Thor B. Nielsen
Attorney Docket Number	CRT/20632 US (4137-04700)

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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
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/Thor Nielsen/ 03/15/2012

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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	Thor B. Nielsen
	Attorney Docket Number	CRT/20632 US (4137-04700)

	1	Office Action dated March 29, 2011 (3 pages) from counterpart application, AU2009243422.	☐
	2	Astelin (azelastine hydrochloride) Nasal Spray, MedPointe Pharmaceuticals, 2006, U.S. Physicians Desk Reference, pp. 1876-1877.	☐
	3	Veramyst (fluticasone furoate) Nasal Spray, GlaxoSmithKline, 2007, Summary Sheet, pp. 1-20.	☐
	4	BARNES, PETER J., "Chronic obstructive pulmonary disease: new opportunities for drug development," Trends in Pharmacological Sciences, Vol. 19, No. 10, 1998, pp. 415-423.	☐
	5	BARNES, PETER J., "Novel approaches and targets for treatment of chronic obstructive pulmonary disease," American Journal of Respiratory and Critical Care Medicine, Vol. 160, 1999, pp. S72-S79.	☐
	6	BARNES, PETER J., "Efficacy of inhaled corticosteroids in asthma," The Journal of Allergy and Clinical Immunology, Vol. 102, No. 4, 1998, pp. 531-538, 1998.	☐
	7	BOWLER, SIMON, "Long acting beta agonists," AUSTRALIAN FAMILY PHYSICIAN, Vol. 27, No. 12, 1998, pp. 1115, 1117-1118, plus cover.	☐
	8	KNOBIL, K., et al., "Adding salmeterol is more effective than increasing the dose of fluticasone for patients with asthma who are symptomatic on low dose fluticasone," European Respiratory Review, Copenhagen, DK, Vol. 12, Suppl. 29, December 1998 (1998-12), pages 19S-20S.	☐
	9	LUMRY, WILLIAM R., "A review of the preclinical and clinical data of newer intranasal steroids in the treatment of allergic rhinitis," Allergy Clin. Immunol., October 1999, 104 (4 Pt 1), pp. S150-S158 plus one correction page.	☐
	10	MELTZER, et al., "Onset of therapeutic effect of fluticasone propionate aqueous nasal spray," Ann. Allergy Asthma Immunol., 2001, Vol. 86, No. 3, pp. 286-291.	☐
	11	MÖLLMANN, H., et al., "Handbook of pharmacokinetic / pharmacodynamic correlation, Chapter 14, Pharmacokinetic-Pharmacodynamic Correlations of Corticosteroids, 323-336, CRC Press, 1995. /Thor Nielsen/	☐

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /T.N./ 03/15/2012

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	Thor B. Nielsen
	Attorney Docket Number	CRT/20632 US (4137-04700)

	12	NAEDELE-RISHA, R., et al., "Dual components of optimal asthma therapy: scientific and clinical rationale for the use of long acting beta-agonists with inhaled corticosteroids," THE JOURNAL OF THE AMERICAN OSTEOPATHIC ASSOCIATION, Vol. 101, No. 9, September 2001, pp. 526-533.	☐
	13	O'CONNER, B. J., "Combination therapy," Pulmonary Pharmacology and Therapeutics, Vol. 11, No. 5/6, 1998, pp. 397-399.	☐
	14	HOLGATE, STEPHEN T., Difficult Asthma, 1999, cover page and publishing information.	☐
	15	PCT/GB01/03495, International Preliminary Examination Report, date of mailing: August 30, 2002.	☐
	16	POPPER, T. L., et al., "Structure-activity relationship of a series of novel topical corticosteroids," Journal of Steroid Biochemistry, 1987, Vol. 27, pp. 837-843.	☐
	17	TANAKA, et al., "Synthesis of 4H-furo[3,2-b]indole derivatives. III (1). Preparation of 4H-furo[3,2-b]indole-2-carboxylic acid derivatives," Journal Heterocyclic Chemistry, Vol. 16, pp. 785-788, 1979.	☐
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	20	Comparative data of azelastine with steroids, 2011.	☐
	21	Malhotra Exhibit B, August 2011.	☐
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	Attorney Docket Number	CRT/20632 US (4137-04700)

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Examiner Signature	/Thor Nielsen/	Date Considered	03/15/2012

*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.

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CERTIFICATION STATEMENT

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

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

OR

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

☐ See attached certification statement.

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

☒ A certification statement is not submitted herewith.

SIGNATURE

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

Signature	/Rodney B. Carroll/	Date (YYYY-MM-DD)	2012-02-23
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.**

/Thor Nielsen/ 03/15/2012

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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).

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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.

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/Thor Nielsen/ 03/15/2012

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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	Thor B. Nielsen
Attorney Docket Number	CRT/20632 US (4137-04700)

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	1	Office Action dated March 29, 2011 (3 pages) from counterpart application, AU2009243422.	☐
	2	Astelin (azelastine hydrochloride) Nasal Spray, MedPointe Pharmaceuticals, 2006, U.S. Physicians Desk Reference, pp. 1876-1877.	☐
	3	Veramyst (fluticasone furoate) Nasal Spray, GlaxoSmithKline, 2007, Summary Sheet, pp. 1-20.	☐
	4	BARNES, PETER J., "Chronic obstructive pulmonary disease: new opportunities for drug development," Trends in Pharmacological Sciences, Vol. 19, No. 10, 1998, pp. 415-423.	☐
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Signature	/Rodney B. Carroll/	Date (YYYY-MM-DD)	2012-02-23
Name/Print	Rodney B. Carroll	Registration Number	39624

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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

Commissioner For Patents
PO Box 1450
Alexandria VA 22313-1450

CERTIFICATE OF FILING

Pursuant to 37 C.F.R. §1.8, I hereby certify that this correspondence is being electronically submitted to the U.S. Patent and Trademark Office website, www.uspto.gov, on 2/23/12.

Edith Shek

Edith Shek

Sir:

SUPPLEMENTAL SUBMISSION

This submission is supplemental to the Information Disclosure Statement filed on December 13, 2011. In response to the Examiner's indication that copies of certain non-patent literature references from the December 13th IDS were of poor quality and therefore could not be fully considered, Applicants respectfully submit herewith supplemental copies of such references. For convenience, the supplemented references are listed in the attached Form PTO/SB/08a. Applicants respectfully request further consideration and admission of these references.

Applicants believe that no fee is necessary for this submission. However, should a fee is deemed necessary, the Commissioner is authorized to charge it to Deposit Account 50-1515 of Conley Rose, P.C. for the filing this Supplemental Information Disclosure Statement.

Respectfully submitted,

Date: 2-23-12

Rodney B. Carroll
Reg. No. 39,624

ATTORNEY FOR APPLICANTS

CONLEY ROSE, P.C.
5601 Granite Parkway, Suite 750
Plano, Texas 75024
(972) 731-2288

Electronic Acknowledgement Receipt

EFS ID:	12145971
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:	CRT/20632 US (4137-04700)
Receipt Date:	23-FEB-2012
Filing Date:	06-JUL-2005
Time Stamp:	18:26:21
Application Type:	U.S. National Stage under 35 USC 371

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4	Non Patent Literature	VERAMYST_Nasal_.pdf	1485814 1c4e85993101d8d9928e66b933a7a17fe56d6a8e	no	21
Warnings:					
Information:					
5	Non Patent Literature	BARNES_Novel_.pdf	1046231 716b91e51a4f684403e923f7ccd4acc73b004bd5	no	8
Warnings:					
Information:					
6	Non Patent Literature	BARNES_Efficacy.pdf	136352 3463c7574d8723e9ed9c567f20d3750dfb9f6230	no	8
Warnings:					
Information:					
7	Non Patent Literature	BOWLER_Long.pdf	428326 36dcdbd314b105794bf1d64b39ba0a3813566300	no	4
Warnings:					
Information:					
8	Non Patent Literature	KNOBIL_Adding.pdf	1460266 f229bb13d6b4d58e187876c86fcb9700146388b3	no	3
Warnings:					
Information:					
9	Non Patent Literature	LUMRY_AReviw_.pdf	1148340 689a3421d4803f7c83fc61e11cf18f805c0f2857	no	10
Warnings:					

Information:					
10	Non Patent Literature	MELTZER_Onset.pdf	167959 1c9970602f72faedeba8962004be54407ed18c8c	no	6
Warnings:					
Information:					
11	Non Patent Literature	MOLLMANN_Handbook.pdf	12571457 c13180c7a82aeb88fb467c29ec2023abaac39621	no	16
Warnings:					
Information:					
12	Non Patent Literature	NAEDELE-RISHA_Dual_.pdf	1105623 04c08ea15711f86f77f50f6afa241fdf8caae589	no	8
Warnings:					
Information:					
13	Non Patent Literature	OCONNER_Combination.pdf	301716 5317dccdcc98e2c41aa64ff1fc2e2c4b03589119	no	3
Warnings:					
Information:					
14	Non Patent Literature	IPER_PCTGB0103495.PDF	567544 82c556208e144a9a2be32cd57519222e5d39fbd0	no	11
Warnings:					
Information:					
15	Non Patent Literature	TANAKA_Synthesis.pdf	496584 0d58136d036092667a6949718d5adfc97fe4cb2a	no	4
Warnings:					
Information:					
16	Non Patent Literature	VANDERMOLEN_Effects.pdf	237202 5b48d155f1d84d0359d9ddd3209ddd016281dd6d	no	6
Warnings:					
Information:					
17	Non Patent Literature	COMPARATIVE_DATA.pdf	217611 e7f177ce5c2f98184a90fdd8593f8247f063e021	no	6
Warnings:					
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Information:					

18	Non Patent Literature	MALHOTRA_ExhibitB.pdf	151475 c6761cbc82facd6bf43329fb1d6d3f4e18c2177c	no	6
Warnings:					
Information:					
19	Non Patent Literature	PETTERSON_Re-evaluatoin.pdf	303871 d1fe33c53cb31da45896f1845908f6d0a782c46a	no	11
Warnings:					
Information:					
20	Non Patent Literature	BARNES_Chronic_Scan.pdf	158296 8cc4ed2ef74550c01262838e2b65f573f6ce5a52	no	9
Warnings:					
Information:					
21	Non Patent Literature	HOLGATE_Difficult_Scan.pdf	1794103 25bf2a35a2307184427cf6144880056cf2ded851	no	3
Warnings:					
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22	Non Patent Literature	POPPER_Structure_Scan.pdf	944991 e8332828591b9f96c0dac92b68faae9458d851e1	no	7
Warnings:					
Information:					
23	Non Patent Literature	UENO_Synthesis_Scan.pdf	2050678 cea5867c1a29e770eb5d391388f9c424c76c67be	no	6
Warnings:					
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24	Transmittal Letter	022312_SupplementalSubmission.pdf	60958 bf97da1235704dc4c1b19953ac3b39f337433a06	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	29983522	

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

UNITED STATES PATENT AND TRADEMARK OFFICE

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

NOTICE OF ALLOWANCE AND FEE(S) DUE

30652 7590 01/30/2012

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

EXAMINER	
NIELSEN, THOR B	
ART UNIT	PAPER NUMBER
1616	

DATE MAILED: 01/30/2012

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

TITLE OF INVENTION: COMBINATION OF AZELASTINE AND STEROIDS

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1740	$300	$0	$2040	04/30/2012

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

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

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

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

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

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

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

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

PART B - FEE(S) TRANSMITTAL

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

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

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

30652 7590 01/30/2012

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

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

Certificate of Mailing or Transmission

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

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

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

TITLE OF INVENTION: COMBINATION OF AZELASTINE AND STEROIDS

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1740	$300	$0	$2040	04/30/2012

EXAMINER	ART UNIT	CLASS-SUBCLASS
NIELSEN, THOR B	1616	514-171000

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

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

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

2. For printing on the patent front page, list

(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____

2 _____

3 _____

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

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

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

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

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

❑ Issue Fee

❑ Publication Fee (No small entity discount permitted)

❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**

❑ A check is enclosed.

❑ Payment by credit card. Form PTO-2038 is attached.

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

❑ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

❑ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

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

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

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

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

30652 7590 01/30/2012

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

EXAMINER	
NIELSEN, THOR B	

ART UNIT	PAPER NUMBER
1616	

DATE MAILED: 01/30/2012

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

The Patent Term Adjustment to date is 434 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 434 day(s).

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

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

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

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.

Supplemental Notice of Allowability	Application No. 10/518,016	Applicant(s) LULLA ET AL.	
	Examiner THOR NIELSEN	Art Unit 1616	

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

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

1. ☒ This communication is responsive to *12/13/2012*.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☒ The allowed claim(s) is/are *1,2,4,6-8,10,13-16,19-22,30,35-38,45 and 53-79*.

4. ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☒ All b) ☐ Some* c) ☐ None of the:
      1. ☒ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

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

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

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

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

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

Attachment(s)

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

Continuation of Attachment(s) 3. Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date: 12/13/2011a; 12/13/2011b; 12/13/2011c.

DETAILED EXAMINATION

Reasons for Allowance

The claims are free of the prior art of record, including references submitted on December 14, 2011 and subsequently reviewed. Further reasons for Allowance were filed on October 3, 2011, and are reiterated by reference.

Status of Claims

Claims 1-2, 4, 6-8, 10, 13-16, 19-22, 30, 35-38, 45, and 53-79 are submitted.

Status of Examination

The Applicant has filed a Request for Continued Examination together with some 350 additional references by Information Disclosure Statements.

Applicant's Claims

Claim 1 is illustrative:

> A pharmaceutical formulation comprising:
> azelastine, or a pharmaceutically acceptable salt thereof, and
> a pharmaceutically acceptable ester of fluticasone,
> wherein said pharmaceutical formulation is in a dosage form suitable for nasal administration.

Conclusion

The portions of the references identified on the three Information Disclosure Statements of December 14, 2011, which were in legible English were reviewed. Illegible text and illegible documents were not reviewed. Also, documents that were not

reasonably identified to correspond to an entry on an Information Disclosure Statement were not reviewed. If the Applicant would like for such documents to be reviewed, appropriately annotated fair copies should be submitted.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to THOR 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
AU 1616

/Johann R. Richter/

Supervisory Patent Examiner, Art Unit 1616

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

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
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.

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	Thor B. Nielsen
Attorney Docket Number	CRT/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
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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]

/Thor Nielsen/

01/13/2012

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	Thor B. Nielsen
	Attorney Docket Number	CRT/20632 US(4137-04700)

	1	Malhotra Exhibit B, August 2011.	☐
	2	Maus Exhibit B, August 2011.	☐
	3	NIELSEN, et al., "Intranasal corticosteroids for allergic rhinitis: superior relief?" Drugs, 2001, Vol. 61, No. 11, pp. 1535-1691.	☐
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	First Named Inventor	Amar Lulla
	Art Unit	1616
	Examiner Name	Thor B. Nielsen
	Attorney Docket Number	CRT/20632 US(4137-04700)

	12	Opponent's submission dated September 23, 2011 regarding list of attendees at oral proceedings on EP Patent No. 1519731.	☐
	13	Opponent's submission dated September 23, 2011 regarding additional documents on EP Patent No. 1519731.	☐
	14	Patentee's submission dated September 19, 2011 on EP Patent No. 1519731.	☐
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Name/Print	Rodney B. Carroll	Registration Number	39624

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	1	0270490	WO		2002-09-12	Glaxo Group Limited		☐
	2	0285296	WO		2002-10-31	Epigenesis Pharmaceuticals, Inc.		☐
	3	8903390	WO		1989-04-20	Bodor		☐

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	4	9015816	WO		1990-12-27	The Upjohn Company		☐
	5	03048181	WO		2003-06-12	Glaxo Group Limited		☐
	6	03072592	WO		2003-09-04	Glaxo Group Limited		☐
	7	9705136	WO		1997-02-13	Boehringer Ingelheim KG		☐
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	26	03066656	WO		2003-08-14	Glaxo Group Limited		☐
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	16	Product Information Rhinocort Aqua (budesonide) Nasal Spray 32 mcg, 2005, pp. 1-2.	☐
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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	Thor B. Nielsen
	Attorney Docket Number	CRT/20632 US(4137-04700)

	27	STEMPEL, et al., "Treatment of allergic rhinitis: an evidence-based evaluation of nasal corticosteroids versus nonsedating antihistamines," Am. J. Man. Care, 1998, Vol. 4, pp. 89-96.	☐
	28	Study No. 03DMW062 - "Pharmacokinetics of GW685698X and CC118781 (fluticasone propionate) when co-administered by the intratracheal or intravenous route to the anaesthetised white pig," 2004.	☐
	29	Study No. B30947 - "The Pharmacokinetics of GW685698X and CC118781 following intratracheal co-administration to the anaesthetised white pig," 2003.	☐
	30	SZEFLER, STANLEY J., et al., Chapter 21, "Glucocorticoids in severe asthma: mechanisms of action and route of administration," DIFFICULT ASTHMA, pp. 371-375, Martin Dunitz Ltd., Informa Health Care, 1999.	☐
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	32	TOGASHI, et al., "9-fluoro-11B, 17, 21-trihyrdroxy-16a-methyl-1,4-pregnadiene-3, 20-dione 21-cyclohexanecarboxylate 17-cyclopropanecarboxylate (ST126); OYO YAKURI, 2002, Vol. 63, No. 5/6, pp. 61-77.	☐
	33	UNEO, et al., "Synthesis and evaluation of antiinflammatory activities of a series of corticosteroid 17. Alpha - esters containing a functional group," JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICA SOCIETY, Vol. 34, No. 8, August 1991, pp. 2468-2473.	☐
	34	UNDEM, et al., "Neural integration and allergic disease," J. Allergy Clin. Immunol., 2000, Vol. 106, No. 5, pp. S213-S220.	☐
	35	The United States Pharmacopoeia, 23rd Ed., US Pharmacopoeia Convention, Inc., Rockville MD, 1995, pp. 1843-1844, "Physical Tests / (941) X-Ray Diffraction."	☐
	36	VAN AS, et al., "Once daily flluticasone propionate is as effective for perennial allergic rhinitis as twice daily beclomethasone dipropionate," J. Allergy Clin. Immunol., 1993, Vol. 91, No. 6, pp. 1146-1154.	☐
	37	VAN BAVEL, et al., "Ocular efficacy and clinician overall evaluation of intranasal fluticasone proprionate (FP) versus loratadine (LOR) in seasonal allergic rhinitis (SAR)," Annals of Allergy, Asthma, & Immunology, 1997, Vol. 78, p. 128, Abstract P101.	☐

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	38	VAN DER MOLEN, et al., "Effects of the long acting beta agonist formoterol on asthma control in asthmatic patients using inhaled corticosteroids," Thorax, Vol. 52, No. 6, 1997, pp. 535-539.	☐
	39	WENKERT, et al., "Short syntheses of furan and catechol derivatives. A synthesis of hydrourushiol1,2," Journal American Chemical Society, Vol. 105, pp. 2021-2029, 1983.	☐
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	43	Notice of Opposition to the grant of patent on Patent Application No. 762/2001 (140397) (Pakistan), 2010.	☐
	44	CIPLA Annual Report Extract; 2010; (report shows that they launched an FF+azelastine product in 2010).	☐
	45	Comparative data of azelastine with steroids, 2011.	☐
	46	Declaration of Geena Malhotra for EP1519731 dated August 11, 2011.	☐
	47	Declaration of Joachim Maus for EP1519731 dated August 10, 2011.	☐
	48	VANRELL, "Preservatives in ophthalmic formulations: an overview," Arch. Soc. Esp. Oftalmol., 2007, Vol. 82, pp. 531-532.	☐
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	Attorney Docket Number	CRT/20632 US(4137-04700)

	49	Malhotra Exhibit A, August 2011.	☐

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☐ See attached certification statement.

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

☒ A certification statement is not submitted herewith.

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Signature	/Rodney B. Carroll/	Date (YYYY-MM-DD)	2011-12-13
Name/Print	Rodney B. Carroll	Registration Number	39624

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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
514	171	09/14/2011	TBN

SEARCH NOTES		
Search Notes	Date	Examiner
East Search	11/4/2009	KB
East Search	11/6/2009	KB
EAST prior art search	09/14/2011	TBN
Review of prior art from new Information Disclosure Statements	01/13/2012	TBN

INTERFERENCE SEARCH			
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First Named Inventor	Amar Lulla
Art Unit	1616
Examiner Name	Thor B. Nielsen
Attorney Docket Number	PAC/20632 US (4137-04700)

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	1	SALIB RAMI JEAN, et al., "Safety and Tolerability Profiles of Intranasal Antihistamines and Intranasal Corticosteroids in the Treatment of Allergic Rhinitis," Drug Safety 2003, Vol. 26, No. 12, Cover page, publication page, pgs. 863-893, ADIS Data Information BV.	☐
	2	SIMPSON, RICHARD J., "Budesonide and terfenadine, separately and in combination, in the treatment of hay fever," Annals of Allergy, December, 1994, Vol. 73, Cover page, publication page, pgs. 497-502.	☐
	3	JUNIPER, E F., et al., "Comparison of beclomethasone dipropionate aqueous nasal spray, astemizone, and the combination in the prophylactic treatment of ragweed pollen-induced rhinoconjunctivitis," Journal of Allergy and Clinical Immunology, March 1989, Vol 83, No. 3, Cover page, Publications page, pgs. 627-633, American Academy of Allergy and Immunology, C.V. Mosby Co.	☐
	4	BARNES, M. L., et al., "Effects of levocetirizine as add-on therapy to fluticasone in seasonal allergic rhinitis," Clinical and Experimental Allergy, January 27, 2006, Vol. 36, pgs. 676-684, Blackwell Publishing Ltd.	☐
	5	Applicants response to foreign communication - EP 03738280.1 (EP Patent 1519731) , September 6, 2010, 15 pages.	☐
	6	File history of Australian Patent Application No. AU2003244799, 38 pages.	☐
	7	File history of Brazilian Patent Application No. PI 0312128-3, 27 pages. April 2011	☐
	8	File history of Canadian Patent Application No. 2,489,427, 19 pages. December 2010	☐
	9	File history of Korean Patent Application No. 10-2004-7020819, 89 pages.	☐
	10	File history of Mexican Patent Application No. PA/a/2004/01266 (now Patent No. 265349), 86 pages.	☐
	11	File history of Polish Patent Application No. P-373001, 95 pages. May 2011	☐

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	12	File history of Russian Patent Application No. RU 2361593 C2, 65 pages. April 2009	☐
	13	File history of South African Patent Application No. 2005/0331 (now Patent No. 2005/0331), 18 pages.	☐
	14	Applicants response to foreign communication - CA 2489427, December 20, 2010, 10 pages.	☐

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Signature	/Rodney B. Carroll/	Date (YYYY-MM-DD)	2011-08-16
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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).

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☐ See attached certification statement.

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

☐ A certification statement is not submitted herewith.

SIGNATURE

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

Signature	/Rodney B. Carroll/	Date (YYYY-MM-DD)	2011-08-22
Name/Print	Rodney B. Carroll	Registration Number	39,624

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/Thor Nielsen/ 09/28/2011

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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	Thor B. Nielsen
Attorney Docket Number	PAC/20632 US (4137-04700)

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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	5232919		1993-08-03	Scheffler, et al.	
	2	5271946		1993-12-21	Hettche	
	3	5658919		1997-08-19	Ratnaraj, et al.	
	4	6319513	B1	2001-11-20	Dobrozsi	
	5	7776315	B2	2010-08-17	Pairet, et al.	
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	1	20040204399	A1	2004-10-14	Osbakken, et al.	
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	1	10152369	DE	A1	2002-05-08	Boehringer Ingelheim Pharma		☐
	2	9746243	WO	A1	1997-12-11	The Procter & Gamble Company		☐
	3	2003244799	AU	B2	2003-12-31	Cipla Limited		☐
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	1	Foreign communication from a related counterpart application - CA2,489,427, Examination Report, June 18, 2010, 3 pages.	☐
	2	Foreign communication from a related counterpart application - CA2,489,427, Examination Report, March 24, 2011, 2 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	Foreign communication from a related counterpart application - Notice of Intent to Grant, EP Application 03738280.1, October 23, 2008, 6 pages.	☐
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	9	GILBERT, PETER, et al., "Preservation of pharmaceutical products," Encyclopedia of Pharmaceutical Technology, 2002, 2nd edition, Vol. 3, pg. 2278 plus cover page and publication page, Marcel Dekker, Inc.	☐
	10	Office Action (Final) dated February 18, 2011 (23 pages), Application Serial No. 12/508,388 filed on July 23, 2009.	☐
	11	Office Action (Final) dated February 24, 2011 (20 pages), Application Serial No. 12/508,393 filed July 23, 2009.	☐
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	23	Duonase Data Sheet, "The Complete Rhinitis Control," 6 pages, Cipla Limited, Mumbai, India. 2004	☐
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	34	World Review 2001: The Pharmaceutical Market, Vol. 1 International, IMS Health, 2001, cover, preface, and copyright pages plus pages 4-42 and 5-1 through 5-11, IMS A.G.	☐
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	45	RATNER, PAUL H., et al., "A Comparison of the Efficacy of Fluticasone Propionate Aqueous Nasal Spray and Loratadine, Alone and in Combination, for the Treatment of Seasonal Allergic Rhinitis," The Journal of Family Practice, August 1998, Vol. 47, No 2, pgs. 118-125, Appleton & Lange.	☐
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Examiner Signature	/Thor Nielsen/	Date Considered	09/28/2011

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/Thor Nielsen/ 09/28/2011

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Issue Classification

Application/Control No.	Applicant(s)/Patent Under Reexamination
10518016	LULLA ET AL.
Examiner	**Art Unit**
THOR NIELSEN	1616

ORIGINAL	
CLASS	SUBCLASS
514	171

CROSS REFERENCE(S)

CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)				

INTERNATIONAL CLASSIFICATION																					
CLAIMED										NON-CLAIMED											
A	0	1	N	45 / 00 (2006.01.01)																	
A	6	1	K	31 / 56 (2006.01.01)																	
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1	1	-	17	-	33	-	49	34	65						
2	2	-	18	-	34	-	50	35	66						
-	3	12	19	17	35	-	51	36	67						
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-	5	14	21	19	37	22	53	38	69						
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-	11	-	27	-	43	28	59	44	75						
-	12	-	28	-	44	29	60	45	76						
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/THOR NIELSEN/ Examiner.Art Unit 1616	01/13/2012	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	48	
/JOHANN RICHTER/ Supervisory Patent Examiner.Art Unit 1616	01/17/2012	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1, 21	None

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10518016	LULLA ET AL.
	Examiner	**Art Unit**
	THOR NIELSEN	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	08/16/2011					
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CLAIM		DATE								
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=	56			✓						

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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	Thor B. Nielsen
Attorney Docket Number	CRT/20632 US(4137-04700)

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	2	6261539		2001-07-17	Adjei, et al.	
	3	4187301		1980-02-05	Edwards	
	4	5972920		1999-10-26	Seidel	
	5	4377575		1983-03-22	Phillipps, et al.	
	6	3856828		1974-12-24	Phillipps, et al.	
	7	4113680		1978-09-12	Kamano, et al.	
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	9	4710495		1987-12-01	Bodor	
	10	5837699		1998-11-17	Sequeira, et al.	
	11	3755302		1973-08-28	Ercoli, et al.	
	12	3557162		1971-01-19	Voorschoten, et al.	
	13	5420120		1995-05-30	Boltralik	
	14	3828080		1974-08-06	May, et al.	
	15	5081113		1992-01-14	Claussner, et al.	
	16	4861765		1989-08-29	Jouveinal	
	17	4267173		1981-05-12	Draper	
	18	4221787		1980-09-09	Bodor, et al.	
	19	5608093		1997-03-04	Stache, et al.	

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	20	4285937		1981-08-25	Kalvoda	
	21	3981894		1976-09-21	Phillipps, et al.	
	22	4261984		1981-04-14	Alvarez	
	23	3639434		1972-02-01	Oxley, et al.	
	24	4188385		1980-02-12	Edwards	
	25	6921757		2005-07-26	Cuenoud, et al.	
	26	4992474		1991-02-12	Skidmore, et al.	
	27	6136294		2000-10-24	Adjei, et al.	
	28	7244742		2007-07-17	Pieper, et al.	
	29	3989686		1976-11-02	Phillipps, et al.	
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	31	2837464		1958-06-03	Nobile	
	32	5889015		1999-03-30	Sequeira, et al.	
	33	4996335		1991-02-26	Bodor	
	34	6197761		2001-03-06	Biggadike, et al.	
	35	6127353		2000-10-03	Yuen, et al.	
	36	5362721		1994-11-08	Stache, et al.	
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	38	5707984		1998-01-13	Tjoeng, et al.	
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	40	3506694		1970-04-14	Oxley	
	41	3067197		1962-12-04	Agnello, et al.	

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	42	4310466		1982-01-12	Edwards	
	43	3312590		1967-04-04	Elks, et al.	
	44	4994439		1991-02-19	Longnecker, et al.	
	45	5658549		1997-08-19	Akehurst, et al.	
	46	5202316		1993-04-13	Claussner, et al.	
	47	6395300		2002-05-28	Straub, et al.	
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	49	4607028		1986-08-19	Schmidlin	
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	51	5981517		1999-11-09	Bodor	
	52	5063222		1991-11-05	Komoto, et al.	

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	53	4472393		1984-09-18	Shapiro	
	54	6330938		2001-12-18	Herve, et al.	
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	7	20040053904	A1	2004-03-18	Komoto, et al.	
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	12	20030144257	A1	2003-07-31	Biggadike, et al.	
	13	20020061281	A1	2002-05-23	Osbakken, et al.	
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	2	0038811	WO		2000-07-06	Glaxo Group Limited		☐
	3	0179583	EP		1986-04-30	Merck & Co. Inc.		☐
	4	889563	BE	A	1981-11-03	Otsuka Pharmaceutical Co., Ltd.		☐
	5	0057401	EP		1982-08-11	Schering Corporation		☐
	6	0178741	WO		2001-10-25	Glaxo Group Limited		☐
	7	0178739	WO		2001-10-25	Glaxo Group Limited		☐
	8	0200679	WO		2002-01-03	Novartis AG, et al.		☐
	9	02088167	WO		2002-11-07	Glaxo Group Limited		☐
	10	0253186	WO		2002-07-11	Roxane Laboratories, Inc.		☐
	11	1384372	GB		1975-02-19	Glaxo Laboratories Limited		☐
	12	0212265	WO		2002-02-14	Glaxo Group Limited		☐

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	13	0178745	WO		2001-10-25	Glaxo Group Limited		☐
	14	0004773	EP		1979-10-17	Syntex (U.S.A.) Inc.		☐
	15	1296458	GB		1972-11-15	Warner-Lambert Company		☐
	16	0251422	WO		2002-07-04	SSP Co., Ltd.		☐
	17	0207767	WO		2002-01-31	Alcon Universal Ltd.		☐
	18	1438940	GB		1976-06-09	Glaxo Laboratories Limited		☐
	19	0154664	WO		2001-08-02	Aeropharm Technology, Inc.		☐
	20	0208243	WO		2002-01-31	Glaxo Group Limited		☐
	21	1517278	GB		1978-07-12	Glaxo Laboratories Limited		☐
	22	1059906	DE		1959-06-25	Scherico Limited		☐
	23	0033892	WO		2000-06-15	Aeropharm Technology, Incorporated		☐

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	24	0120331	WO		2001-03-22	Xenoport, Inc.		☐
	25	8291073	JP		1996-11-05	Kissei Pharmaceutical Co. Ltd.		☐
	26	109656	IL		1998-02-22	Chemagis Ltd.		☐
	27	2079755	GB		1982-01-27	Otsuka Parmaceutical Company Limited		☐
	28	0393658	EP		1990-10-24	SS Pharmaceutical Co., Ltd.		☐
	29	0266422	WO		2002-08-29	Glaxo Group Limited		☐
	30	02100879	WO		2002-12-19	Glaxo Group Limited		☐
	31	0200199	WO		2002-01-03	Glaxo Group Limited		☐
	32	0213868	WO		2002-02-21	Glaxo Group Limited		☐
	33	0226723	WO		2002-04-04	Glaxo Group Limited		☐
	34	8291072	JP		1996-11-05	Kissei Pharmaceutical Co. Ltd.		☐

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	35	0066522	WO		2000-11-09	Pfizer Products Inc.		☐
	36	0049993	WO		2000-08-31	Nitromed, Inc.		☐
	37	0212266	WO		2002-02-14	Glaxo Group Limited		☐
	38	0416951	EP		1991-03-13	Glaxo Group Limited		☐
	39	0202565	WO		2002-01-10	Abbott Laboratories		☐
	40	0178736	WO		2001-10-25	Glaxo Group Limited		☐
	41	0016814	WO		2000-03-30	Aeropharm Technology Incorporated		☐
	42	2140800	GB		1984-12-05	Glaxo Group Limited		☐
	43	04208267	JP		1992-07-29	Mitsui Petrochem Ind. Ltd.		☐
	44	0236106	WO		2002-05-10	Boehringer Ingelheim Pharma KG		☐
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	46	0154481	WO		2001-08-02	Rohm and Haas Company		☐
	47	1191965	GB		1970-05-13	Warner-Lambert Pharmaceutical Company		☐
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	1	"Azelastine," STN Registry No. 58581-89-8, STN Registry File, Retrieved 2010-11-23, page 1.	☐
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	5	Astepro (azelastine HCl) Nasal Spray 0.15%, Meda Pharmaceuticals Inc., 2009, Press Release, pp. 1-4.	☐
	6	AIGBIRHIO, FRANKLIN I., et al., "Automated radiosynthesis of no-carrier-added [S-fluoromethyl-18F]Fluticasone propionate as a radiotracer for lung deposition studies with PET," Journal of Labelled Compounds and Radiopharmaceuticals, Vol. 39, No. 7, 1997, pp. 569-584.	☐
	7	AUSTIN, et al., "Mometasone furoate is a less specific glucocorticoid than fluticasone propionate," Eur. Respir. J., 2002, Vol. 20, pp. 1386-1392.	☐
	8	BANOV, et al., "Once daily intranasal fluticasone propionate is effective for perennial allergic rhinitis," Annals of Allergy, 1994, Vol. 73, pp. 240-246.	☐
	9	BARNES, PETER J., "Chronic obstructive pulmonary disease: new opportunities for drug development," Trends in Pharmacological Sciences, Vol. 19, No. 10, 1998, pp. 415-423.	☐
	10	BARNES, PETER J., "Novel approaches and targets for treatment of chronic obstructive pulmonary disease," American Journal of Respiratory and Critical Care Medicine, Vol. 160, 1999, pp. S72-S79.	☐
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	12	BAUMGARTEN, C., et al., "Initial treatment of symptomatic mild to moderate bronchial asthma with the salmeterol/ fluticasone propionate (50/250µg) combination product (SAS 40023)," European Journal of Medical Research, 2002, Vol. 7, pp. 1-7.	☐
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	16	BRYSON, et al., "Intranasal fluticasone propionate: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in allergic rhinitis," Drugs, 1992, Vol. 43, No. 5, pp. 760-775.	☐
	17	BUSSE, WILLIAM, et al., "Steroid-sparing effects of fluticasone propionate 100µg and salmeterol 50 µg administered twice daily in a single product in patients previously controlled with fluticasone propionate 250 µg administered twice daily," J. Allergy Clin. Immunol., Vol. 111, No. 1, January 2003, pp. 57-65.	☐
	18	CAS Registry No. 102113-40-6, 2004.	☐
	19	CAS Registry No. 90566-53-3, "Fluticasone," November 16, 1984.	☐
	20	CHAPMAN, et al., "Anti-inflammatory activity of inhaled mometasone furoate in allergic mice," Arzneimettelforschung ("Drug Research"), 1998, Vol. 48, No. 4, pp. 384-391.	☐
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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	Thor B. Nielsen
	Attorney Docket Number	CRT/20632 US(4137-04700)

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Examiner Name	Thor B. Nielsen
Attorney Docket Number	CRT/20632 US(4137-04700)

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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).

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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)	2011-12-13
Name/Print	Rodney B. Carroll	Registration Number	39624

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EFS ID:	11600046
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:	CRT/20632 US (4137-04700)
Receipt Date:	13-DEC-2011
Filing Date:	06-JUL-2005
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Application Type:	U.S. National Stage under 35 USC 371

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	2	0285296	WO		2002-10-31	Epigenesis Pharmaceuticals, Inc.		☐
	3	8903390	WO		1989-04-20	Bodor		☐

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	4	9015816	WO		1990-12-27	The Upjohn Company		☐
	5	03048181	WO		2003-06-12	Glaxo Group Limited		☐
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	11	03035668	WO		2003-05-01	Glaxo Group Limited		☐
	12	03000241	WO		2003-01-03	Boehringer Ingelheim Pharma KG		☐
	13	03064445	WO		2003-08-07	Glaxo Group Limited		☐
	14	872389	ZA		1987-04-02	Advanced Polymer Systems, Incorporated		☐

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	Examiner Name	Thor B. Nielsen
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	15	9901467	WO		1999-01-14	Glaxo Group Limited		☐
	16	03086399	WO		2003-10-23	Boehringer Ingelheim GmbH & Co. KG		☐
	17	9715298	WO		1997-05-01	Bayer Aktiengesellschaft		☐
	18	03033000	WO		2003-04-24	Glaxo Group Limited		☐
	19	03062259	WO		2003-07-31	Glaxo Group Limited		☐
	20	9531964	WO		1995-11-30	Glaxo Australia Pty. Limited		☐
	21	03040691	WO		2003-05-15	The Brigham and Women's Hospital, Inc.		☐
	22	9104252	WO		1991-04-04	Boehringer Ingelheim International GmbH, et al.		☐
	23	9619199	WO		1996-06-27	Astra Aktiebolag		☐
	24	9724365	WO		1997-07-10	Glaxo Group Limited		☐
	25	9834596	WO		1998-08-13	Minnesota Mining and Manufacturing Company		☐

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	26	03066656	WO		2003-08-14	Glaxo Group Limited		☐
	27	9721724	WO		1997-06-19	G.D. Searle & Co.		☐
	28	04013156	WO		2004-02-12	Novartis AG		☐
	29	03013427	WO		2003-02-20	SmithKline Beecham Corporation		☐
	30	0276933	WO		2002-10-03	Glaxo Group Limited		☐
	31	9721721	WO		1997-06-19	G.D. Searle & Co.		☐
	32	9740836	WO		1997-11-06	G.D. Searle & Co.		☐
	33	9925359	WO		1999-05-27	Astra Aktiebolag		☐
	34	03042229	WO		2003-05-22	Glaxo Group Limited		☐
	35	9932089	WO		1999-07-01	Astra Aktiebolag		☐
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	37	03066033	WO		2003-08-14	Glaxo Group Limited		☐
	38	03066036	WO		2003-08-14	Glaxo Group Limited		☐
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	40	2004019955	WO	A1	2004-03-11	Altana Pharma AG		☐
	41	2008012338	WO	A2	2008-01-31	Glaxo Group Limited		☐

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	49	Malhotra Exhibit A, August 2011.	☐

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Signature	/Rodney B. Carroll/	Date (YYYY-MM-DD)	2011-12-13
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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
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26	Foreign Reference	WO200366656.pdf	6131885 e507f1821081329a4f9e748ea7544b460ebcd731	no	118
Warnings:					
Information:					
27	Foreign Reference	WO9721724.pdf	1189373 b523f5b2f10116560aad45be274acf9caccc677e	no	42
Warnings:					
Information:					
28	Foreign Reference	WO200413156.pdf	773562 33725d201eb5d73a60ec2ba690a3d4b1f939385b	no	20
Warnings:					
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29	Foreign Reference	WO200313427.pdf	1149476 796ff6b219ff30c63347224e957b6d05e7a546cc	no	27
Warnings:					
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30	Foreign Reference	WO200276933.pdf	1718841 ce4a27ac861f5c6b30428a3bfefe46dfb166b967	no	41
Warnings:					
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31	Foreign Reference	WO9721721.pdf	1661260 1749f780439188abb4137806a01ec40c8a2021cf	no	53
Warnings:					
Information:					
32	Foreign Reference	WO9740836.pdf	1453945 56236db1d7eb370e42ee9aeacb1615d492dd8427	no	47
Warnings:					
Information:					
33	Foreign Reference	WO9925359.pdf	1116855 11b68215d619b4acc028b21207fb70babb60a13d	no	29
Warnings:					
Information:					
34	Foreign Reference	WO200342229.pdf	1653472 fd03fc62e12122e83e96293aa011c09679cb29ed	no	39
Warnings:					
Information:					
35	Foreign Reference	WO9932089.pdf	794487 1b9bb43869d70524fb68135b5a37adc5fb65b7db	no	20
Warnings:					
Information:					
36	Foreign Reference	WO9632151.pdf	1012543 6ea0849fdcb439faed6fa4547469b11d958729ea	no	25
Warnings:					
Information:					
37	Foreign Reference	WO200366033.pdf	3153573 33ab12636891a5d1ee339700763db2011ce16638	no	72
Warnings:					
Information:					

38	Foreign Reference	WO200366036.pdf	3263491 78a02d1816d611f732bb8759f6169595251b9e36	no	78
Warnings:					
Information:					
39	Foreign Reference	EP-780127.pdf	488638 e8b39f3c9b2213330a368f6805841364bfe99f0d	no	9
Warnings:					
Information:					
40	Foreign Reference	WO2004019955.pdf	852005 d43f55ef02e0a7f3539460531e20f4f61263ea2d	no	18
Warnings:					
Information:					
41	Foreign Reference	WO2008012338.pdf	828732 7baae41807d7375a2fed25cd1a3f3201209d3a09	no	26
Warnings:					
Information:					
42	Non Patent Literature	Mollmann_Pharmacokinetic.pdf	769931 5912c6d1ee2032e6a8970e3e99ddf2572885633c	no	16
Warnings:					
Information:					
43	Non Patent Literature	Vargas_Synthesis.pdf	855048 c9250c310a952a9359bc5035ecdb9ec733b55d65	no	20
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44	Non Patent Literature	Naedele-Risha_DualComponents.pdf	1243316 ca3f0a2c5066bac215950699486cdd04f4cd3d63	no	8
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45	Non Patent Literature	Nathan_AOnceDaily.pdf	514431 fbe99aa9188bec00280199dc120371026a5b8028	no	7
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46	Non Patent Literature	Nelson_Fluticasone.pdf	622126 7de0c0047cc3c75976a24fe0e7b5e08cfe3c6161	no	8
Warnings:					
Information:					

47	Non Patent Literature	OConnor_CombinationTherapy.pdf	350372 09263a1ad5fd0aa2ce0256c5bd6e4e79e981c034	no	3
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48	Non Patent Literature	Ong_Micellar.pdf	290287 3d253b25b8af8f3af84e4781a5252f2580496d85	no	5
Warnings:					
Information:					
49	Non Patent Literature	Ong_IntrinsicPotencies.pdf	251453 fcba8e1060c8dcdf05724a2a381f1e040ab2037c	no	4
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50	Non Patent Literature	Onrust_Mometasone.pdf	1481662 5988d7acc608ee6753ef7b751f16dc610375b43a	no	21
Warnings:					
Information:					
51	Non Patent Literature	HOLGATE_Difficult.pdf	552116 db946954f457ebd6889e6d4d5ad4d2efc61b40db	no	2
Warnings:					
Information:					
52	Non Patent Literature	083002_IPER_PCTGB0103495.pdf	563769 76dbfe751ff368e472c5086a04c09fb375fa7505	no	11
Warnings:					
Information:					
53	Non Patent Literature	PETTERSON_Re-evaluatoin.pdf	303871 d1fe33c53cb31da45896f1845908f6d0a782c46a	no	11
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Information:					
54	Non Patent Literature	PHILLIPS_Synthesis.pdf	1382783 42e5342b7c22f1586df897885f7c589f80d01ac4	no	13
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Information:					
55	Non Patent Literature	POPPER_Structure.pdf	248217 29a2679aee8e6f7b28d7b60956d297cf1ccede22	no	7
Warnings:					
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56	Non Patent Literature	ProductInformation_Flonase.pdf	431706 4e994ddae4face86e21a970f096f48e6af1723cf	no	13
Warnings:					
Information:					
57	Non Patent Literature	RhinocortAqua32.pdf	349498 4b483726fef6f00f39ee9c85e2a35d867e4b2b3e	no	2
Warnings:					
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58	Non Patent Literature	SAKAGAMI_Mucoadhesive.pdf	365673 38f12f6166d520f960d18ecdc1955ba8b0ba0127	no	7
Warnings:					
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59	Non Patent Literature	SANDHAM_Synthesis.pdf	1012507 50d7aa5b34861cafd80758cfe704671d016ff8ad	no	12
Warnings:					
Information:					
60	Information Disclosure Statement (IDS) Form (SB08)	121311_IDS_Form2.pdf	618118 ff4d9fa1eb896adff8ca407da969f9265039a08a	no	12
Warnings:					
Information:					

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

Total Files Size (in bytes):	86471044

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

New Applications Under 35 U.S.C. 111

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

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

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

New International Application Filed with the USPTO as a Receiving Office

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

UNITED STATES PATENT AND TRADEMARK OFFICE

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

NOTICE OF ALLOWANCE AND FEE(S) DUE

30652 7590 10/03/2011

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

EXAMINER
NIELSEN, THOR B

ART UNIT	PAPER NUMBER
1616	

DATE MAILED: 10/03/2011

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

TITLE OF INVENTION: COMBINATION OF AZELASTINE AND STEROIDS

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1740	$300	$0	$2040	01/03/2012

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

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

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

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

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

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

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

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

PART B - FEE(S) TRANSMITTAL

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

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

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

30652 7590 10/03/2011

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

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

Certificate of Mailing or Transmission

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

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

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

TITLE OF INVENTION: COMBINATION OF AZELASTINE AND STEROIDS

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1740	$300	$0	$2040	01/03/2012

EXAMINER	ART UNIT	CLASS-SUBCLASS
NIELSEN, THOR B	1616	514-171000

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

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

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

2. For printing on the patent front page, list

(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____

2 _____

3 _____

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

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

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

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

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

❑ Issue Fee

❑ Publication Fee (No small entity discount permitted)

❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**

❑ A check is enclosed.

❑ Payment by credit card. Form PTO-2038 is attached.

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

❑ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

❑ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

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

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

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

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

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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P.O. Box 1450
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www.uspto.gov

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

30652 7590 10/03/2011

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

EXAMINER	
NIELSEN, THOR B	

ART UNIT	PAPER NUMBER
1616	

DATE MAILED: 10/03/2011

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

The Patent Term Adjustment to date is 434 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 434 day(s).

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

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

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

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.

Examiner-Initiated 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)_____.

(2) *Mr. Rodney Carroll*. (4)_____.

Date of Interview: *09 September 2011*.

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

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

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

Claim(s) discussed: _____.

Identification of prior art discussed: _____.

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

Mr. Carroll agreed to the proposed Examiner's Amendment. In a separate call on September 14, 2011, Mr. Carroll agreed to an additional proposed Examiner's Amendment.

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

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

☐ Attachment

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

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

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

1. ☒ This communication is responsive to *08/22/2011*.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☒ The allowed claim(s) is/are *1,2,4,6-8,10,13-16,19-22,30,35-38,45 and 53-79*.

4. ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☒ All b) ☐ Some* c) ☐ None of the:
      1. ☒ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

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

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

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

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

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

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date See Continuation Sheet
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☒ Interview Summary (PTO-413), Paper No./Mail Date *20110906* .
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

Continuation of Attachment(s) 3. Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date: 08/16/2011(a); 08/16/2011(b); 08/22/2011.

DETAILED ACTION

Examiner's Amendment

EXAMINER'S AMENDMENT

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

The application has been amended as follows:

In claim 1, immediately after *pharmaceutically acceptable salt* the text: ", solvate or physiologically functional derivative" has been deleted.

In claim 7, immediately after *pharmaceutically acceptable salt* the text: ", solvate or physiologically functional derivative" has been deleted.

In claim 8, immediately after *pharmaceutically acceptable salt* the text: ", solvate or physiologically functional derivative" has been deleted.

In claim 16, immediately after *tragacanth* the text: "ethoxose (water soluble binding and thickening agents on the basis of ethyl cellulose)," has been deleted.

In claim 45, immediately after *pharmaceutically acceptable salt* the text: ", solvate or physiologically functional derivative" has been deleted.

In claim 56, immediately after *pharmaceutically acceptable salt* the text: ", solvate or physiologically functional derivative" has been deleted.

In claim 64, immediately after *formulation of claim* the text "60" has been deleted and "56" substituted in its place.

In claim 65, immediately after *formulation of claim* the text "61" has been deleted and "56" substituted in its place.

Authorization for this examiner's amendment was given in a telephone interview with Mr. Carroll on September 9, 2011. A second examiner's amendment was authorized in a telephone interview with Mr. Carroll on September 14, 2011.

Reasons for Allowability

The Declaration under Rule 132 by Mr. Copra (the Chopra Declaration) is of proper legal form and provides the sales figures of Duonase™ (which he states is the commercial embodiment of the claimed invention) and copycat products for seven years. The data support the commercial success of Duonase. *At* items 7-9 and Table II. The first year of sales were over 167,000 units and the second year sales were over 254,000 units. Id. By year seven, sales were in excess of 918,000 units. Id. Competitors arose in year 2 (Zydus-Cadila and Sun Pharma), year 3 (Lupin Ltd.), year 4 (Entod), year 6 (Ranbaxy), and year 7 (Intas Pharma and Dr. Reddys Labs). Id. In year 7, the competitors sold in excess of 408,000 units, by my calculation. That is, the competitors commanded almost 45% of the market share. Figure 3. The major copy products were combinations of fluticasone propionate and azelastine HCl. Table I. The market growth rate over the seven years has been about 20 % annually and the sales of Duonase have grown at essentially the same pace. *At* item 12.

More specifically, Duonase has maintained a sales growth consistent with the sales growth of the overall market for these nasal sprays and not unexpectedly is gradually losing potential sales as more competitors offer similar products.

Thus, the Chopra Declaration supports that the product of the invention has been a commercial success for both the inventors and the copiers.

Moreover, the Chopra Declaration also supports that the product of the invention has filled a long-felt, but unmet need for an improved treatment for allergic rhinitis.

The Declaration under Rule 132 by Dr. Rajan also supports that the invention fills a long unmet need. Dr. Rajan states that prior to introduction of the formulation of the instant invention (Duonase), he prescribed nasal ***corticosteroids alone*** for patients having allergic and non-allergic vasomotor rhinitis. *At* item 9. Dr. Rajan continues that nasal steroids are an effective medication for allergic rhinitis and are slow to act so that patient compliance is a problem. *At* item 10. He continues that oral anti-histamines have side effects such as sedation, whether taken alone or in conjunction with nasal steroids. *At* items 11 and 12. He concludes that Duonase (the inventive formulation) solves many of the long term problems and provides superior and almost immediate relief from the symptoms of allergic rhinitis. *At* items 13-14.

Dr. Maus, in a Declaration under Rule 132, reviews several literature studies that examined possible benefits of combining nasal steroid with an ***oral*** antihistamine and reports that the studies found no clinical benefit or minimal clinical benefit to this combination therapy. *At* items 18-21. Moreover, he reviews a non-prior art study which concludes that there is no evidence that combining intranasal corticosteroids and

intranasal antihistamines provides any additional therapeutic benefit, in comparison with intranasal steroids alone. *At* item 22. Thus, Dr. Maus concludes that the superior results obtained with the combination of nasal fluticasone propionate and azelastine HCl would have been unexpected at the time of filing of the application. *At* item 23. On the basis of this information and declaration, the examiner concurs in this conclusion.

Dr. Maus also states that a randomized, double-blind placebo-controlled clinical study was performed having 610 patients was carried out. *At* items 7-8. The antigen was the Texas Mountain cedar. Id. One spray per nostril was administered twice daily to provide total doses of 548 ug azelastine HCl and 200 ug fluticasone HCl [sic, propionate]. Id. Patients were scored by the 12 hour reflective total nasal symptom score (rTNSS) on a four-point scale. A 50% reduction of rTNNS was considered clinically relevant. Id. After 2 weeks, the combination therapy reduced the mean rTNSS by a significantly greater extent than either azelastine HCl monotherapy ($p<0.001$), fluticasone HCl [sic] monotherapy ($p=0.003$), or placebo ($p<0.001$). *At* item 9. A 50% reduction was achieved by 49% of the combination therapy patients, which exceeded the response with azelastine HCl (37% of patients), fluticasone propionate (38% of patients), and placebo (28 % of patients). *At* item 10. These results were significant. *At* item 11. The combination therapy effect was observed 5-6 days earlier than the other treatments. Id. Dr. Maus also reported a separate randomized, double-blind placebo-controlled clinical study of 779 patients using the same therapeutic nasal sprays, but reviewing ocular symptoms. *At* items 12-16. The combination therapy was significantly better at relieving ocular symptoms than the fluticasone propionate

monotherapy or the placebo and trended better than azelastine HCl monotherapy. Id. The examiner finds that the clinical trial supports the efficacy of the treatment composition of the invention and that the composition is superior to the tested monotherapies and to the placebo.

The Declarations by Dr. Rajan and Dr. Maus are of proper legal form.

Thus, the invention is unexpectedly and surprisingly unobvious over, different from, and superior to the prior art of record.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to THOR 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
AU 1616

/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	Thor B. Nielsen
Attorney Docket Number	PAC/20632 US (4137-04700)

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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	5232919		1993-08-03	Scheffler, et al.	
	2	5271946		1993-12-21	Hettche	
	3	5658919		1997-08-19	Ratnaraj, et al.	
	4	6319513	B1	2001-11-20	Dobrozsi	
	5	7776315	B2	2010-08-17	Pairet, et al.	
	6	5914122		1999-06-22	Otterbeck, et al.	
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	1	20040204399	A1	2004-10-14	Osbakken, et al.	
	2	20040235807	A1	2004-11-25	Weinrich, et al.	

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	1	10152369	DE	A1	2002-05-08	Boehringer Ingelheim Pharma		☐
	2	9746243	WO	A1	1997-12-11	The Procter & Gamble Company		☐
	3	2003244799	AU	B2	2003-12-31	Cipla Limited		☐
	4	2002-053485	JP		2002-02-19	Oshida Tetsuo		☐

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	1	Foreign communication from a related counterpart application - CA2,489,427, Examination Report, June 18, 2010, 3 pages.	☐
	2	Foreign communication from a related counterpart application - CA2,489,427, Examination Report, March 24, 2011, 2 pages.	☐
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	4	Foreign communication from a related counterpart application - Examination Report, EP Application 03738280.1, July 18, 2007, 5 pages.	☐
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	6	Foreign communication from a related counterpart application - AU2003244799, Examination Report, November 20, 2007, 2 pages.	☐
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	11	Office Action (Final) dated February 24, 2011 (20 pages), Application Serial No. 12/508,393 filed July 23, 2009.	☐
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	~~23~~	~~Duonase Data Sheet, "The Complete Rhinitis Control," 6 pages, Cipla Limited, Mumbai, India.~~	☐
	24	DROUIN, MICHEL A., et al., "Adding Loratadine to Topical Nasal Steroid Therapy Improves Moderately Severe Seasonal Allergic Rhinoconjunctivitis," Advances in Therapy, Vol. 12, No. 6, November/December 1995, pgs. 340 - 349, Health Communications Inc.	☐
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	26	HODGES, N. A., et al., "Preservative Efficacy Tests in Formulated Nasal Products: Reproducibility and Factors Affecting Preservative Activity," J. Pharm. Pharmacol., 1996, Vol. 48, pgs. 1237-1242.	☐
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	28	Prescribing Information for Astepro®, November 2010, 20 pages, Meda Pharmaceuticals Inc., Somerset, NJ, US.	☐
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	33	WISEMAN, LYNDA R., et al., "Intranasal Fluticasone Propionate: A Reappraisal of its Pharmacology and Clinical Efficacy in the Treatment of Rhinitis," Drugs, 1997, Vol. 53, No. 5, pgs. 885-907, Adis International Limited. /Thor Nielsen/ 09/23/2011	☐

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	34	World Review 2001: The Pharmaceutical Market, Vol. 1 International, IMS Health, 2001, cover, preface, and copyright pages plus pages 4-42 and 5-1 through 5-11, IMS A.G.	☐
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	37	~~Product Specification Bulletin, Avicel® RC-591, Bulletin AVC591-SPEC-02/09 RS, 2 pages, FMC BioPolymer.~~	☐
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	44	RATNER, PAUL H., et al., "Combination therapy with azelastine hydrochloride nasal spray and fluticasone propionate nasal spray in the treatment of patients with seasonal allergic rhinitis," Annals of Allergy, Asthma & Immunology, January 2008, Vol. 100, Cover page, publishing page, pgs. 74-81. /Thor Nielsen/ 09/23/2011	☐

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	48	DI LORENZO, G., et al., "Randomized Placebo-controlled Trial Comparing fluticasone aqueous nasal spray in mono-therapy, fluticasone plus cetirizine, fluticasone plus montelukast and cetirizine plus montelukast for seasonal allergic rhinitis," Clin. Exp. Allergy, 2004, Vol. 34, pgs. 259-267, Blackwell Publishing Ltd.	☐
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	50	HOWARTH, P. H., "A comparison of the anti-inflammatory properties of intranasal corticosteroids and antihistamines in allergic rhinitis," Allergy 2000, Vol. 62, pgs. 6-11, Munksgaard 2000.	☐

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EXAMINER SIGNATURE

Examiner Signature	/Thor Nielsen/	Date Considered	09/23/2011

*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.

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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)	2011-08-16
Name/Print	Rodney B. Carroll	Registration Number	39,624

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/Thor Nielsen/ 09/23/2011

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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.

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/Thor Nielsen/ 09/23/2011

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EAST Search History

EAST Search History (Prior Art)

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L5	7276	fluticasone	US-PGPUB; USPAT; USOCR	OR	ON	2011/09/14 09:58
L7	51	L1 AND L5	US-PGPUB; USPAT; USOCR	OR	ON	2011/09/14 09:58
L8	6	L1 AND L5 AND azelastine	US-PGPUB; USPAT; USOCR	OR	ON	2011/09/14 09:58
S1	4217	fluticasone SAME (propionate valerate)	US-PGPUB; USPAT; USOCR	OR	ON	2011/02/03 19:29
S2	538	(fluticasone SAME (propionate valerate)) AND (nasal NEAR3 (spray drop))	US-PGPUB; USPAT; USOCR	OR	ON	2011/02/03 19:30
S3	149	(fluticasone SAME (propionate and valerate)) AND (nasal NEAR3 (spray drop))	US-PGPUB; USPAT; USOCR	OR	ON	2011/02/03 19:31
S4	6	(fluticasone NEAR3 (propionate and valerate)) AND (nasal NEAR3 (spray drop))	US-PGPUB; USPAT; USOCR	OR	ON	2011/02/03 19:34
S5	15	(fluticasone NEAR3 (valerate)) AND (nasal NEAR3 (spray drop))	US-PGPUB; USPAT; USOCR	OR	ON	2011/02/03 19:35
S6	512	(fluticasone NEAR3 (propionate)) AND (nasal NEAR3 (spray drop))	US-PGPUB; USPAT; USOCR	OR	ON	2011/02/03 19:37
S7	125583	(S-(fluoromethyl) NEAR20 difluoro NEAR20 octahydrocyclopenta NEAR20 phenanthrene NEAR20 carbothioate) AND (valerate propionate)	US-PGPUB; USPAT; USOCR	OR	ON	2011/02/03 19:48
S8	19676	(S-(fluoromethyl) NEAR20 difluoro NEAR20 octahydrocyclopenta NEAR20 phenanthrene NEAR20 carbothioate) AND (valerate propionate) AND steroid	US-PGPUB; USPAT; USOCR	OR	ON	2011/02/03 19:48
S9	19676	(S-(fluoromethyl) NEAR20 difluoro NEAR20 octahydrocyclopenta NEAR6	US-PGPUB;	OR	ON	2011/02/03 19:49

		phenanthrene NEAR6 carbothioate) AND (valerate propionate) AND steroid	USPAT; USOCR			
S10	0	((fluoromethyl) NEAR20 difluoro NEAR20 octahydrocyclopenta NEAR6 phenanthrene NEAR6 carbothioate) AND (valerate propionate) AND steroid	US-PGPUB; USPAT; USOCR	OR	ON	2011/02/03 19:49
S11	0	((fluoromethyl) NEAR20 difluoro NEAR20 octahydrocyclopenta NEAR6 phenanthrene NEAR6 carbothioate) AND (valerate propionate)	US-PGPUB; USPAT; USOCR	OR	ON	2011/02/03 19:50
S12	0	((fluoromethyl) NEAR20 difluoro NEAR20 octahydrocyclopenta NEAR10 phenanthrene NEAR10 carbothioate) AND (valerate propionate)	US-PGPUB; USPAT; USOCR	OR	ON	2011/02/03 19:50
S13	76	fluticasone AND valerate	EPO; JPO; DERWENT	OR	ON	2011/02/03 20:00
S14	43	fluticasone NEAR10 valerate	EPO; JPO; DERWENT	OR	ON	2011/02/03 20:00
S15	33	S13 NOT S14	EPO; JPO; DERWENT	OR	ON	2011/02/03 20:11
S16	1	"6294153".pn.	US-PGPUB; USPAT; USOCR	OR	ON	2011/02/03 20:14
S17	18	("20020076382" | "20040136918" | "20040242638" | "20050192261" | "20060110331" | "20060228306" | "20070020330" | "20090291143" | "20090318397" | "20100152147" | "4335121" | "5164194" | "6017963" | "6294153" | "6391340" | "6416743" | "6583180" | "6787532").PN.	US-PGPUB; USPAT; USOCR	OR	ON	2011/02/09 14:23
S18	1	("20080131381").PN.	US-PGPUB; USPAT; USOCR	OR	ON	2011/02/09 17:23
S19	1	wo-9826808-$.did.	DERWENT	OR	OFF	2011/06/16 10:45
S20	1	"20030203009".pn.	US-PGPUB; USPAT; USOCR	OR	OFF	2011/06/16 11:14
S21	0	(macdonald NEAR3 gavin).in. AND (martin).in.	DERWENT	OR	OFF	2011/06/16 11:20
S22	43	(macdonald).in. AND (martin).in.	DERWENT	OR	OFF	2011/06/16 11:21
S23	4	(macdonald).in. AND (martin).in. AND (kim).in.	DERWENT	OR	OFF	2011/06/16 11:21
S24	1	gb-2257428-$.did.	DERWENT	OR	OFF	2011/06/16 15:50
S25	2	"6294153".pn. "6416743".pn.	USPAT	OR	OFF	2011/08/01 10:19
S26	745	fluticasone WITH (valerate)	US-PGPUB; USPAT; USOCR	OR	ON	2011/09/06 14:22
S27	258	fluticasone WITH (valerate) AND	US-	OR	ON	2011/09/06

		(@pd<"20030613" or @ad<"20030613" or @prad<"20030613" or @rlad<"20030613" or @ptad<"20030613")	PGPUB; USPAT; USOCR			14:24
S28	129	fluticasone WITH (valerate) AND (@pd<"20030613" or @ad<"20030613" or @prad<"20030613" or @rlad<"20030613" or @ptad<"20030613") AND (nasal nose)	US-PGPUB; USPAT; USOCR	OR	ON	2011/09/06 14:24
S29	13	fluticasone NEAR6 (valerate) AND (@pd<"20030613" or @ad<"20030613" or @prad<"20030613" or @rlad<"20030613" or @ptad<"20030613") AND (nasal nose)	US-PGPUB; USPAT; USOCR	OR	ON	2011/09/06 14:25
S30	0	fluticasone NEAR6 (valerate) AND (@pd<"20030613" or @ad<"20030613" or @prad<"20030613" or @rlad<"20030613" or @ptad<"20030613") AND (nasal nose)	EPO; JPO; DERWENT	OR	ON	2011/09/06 15:00
S31	9	fluticasone NEAR6 (valerate) AND (@pd<"20030613" or @ad<"20030613" or @prad<"20030613" or @rlad<"20030613" or @ptad<"20030613")	EPO; JPO; DERWENT	OR	ON	2011/09/06 15:00
S32	0	((microcrystalline NEAR3 cellulose) AND (carboxymethyl NEAR3 cellulose) AND ((phenyl ADJ ethyl ADJ alcohol) phenyl ADJ ethanol)) AND (@pd<"20030613" or @ad<"20030613" or @prad<"20030613" or @rlad<"20030613" or @ptad<"20030613")	EPO; JPO; DERWENT	OR	ON	2011/09/06 17:11
S33	139	((microcrystalline NEAR3 cellulose) AND (carboxymethyl NEAR3 cellulose) AND ((phenyl ADJ ethyl ADJ alcohol) phenyl ADJ ethanol)) AND (@pd<"20030613" or @ad<"20030613" or @prad<"20030613" or @rlad<"20030613" or @ptad<"20030613")	US-PGPUB; USPAT; USOCR	OR	ON	2011/09/06 17:11
S34	62	((microcrystalline NEAR3 cellulose) AND (carboxymethyl NEAR3 cellulose) AND ((phenyl ADJ ethyl ADJ alcohol) phenyl ADJ ethanol)) AND (@pd<"20030613" or @ad<"20030613" or @prad<"20030613" or @rlad<"20030613" or @ptad<"20030613") AND (nasal nose)	US-PGPUB; USPAT; USOCR	OR	ON	2011/09/06 17:12
S35	44	((microcrystalline NEAR3 cellulose) AND (carboxymethyl NEAR3 cellulose) AND ((phenyl ADJ ethyl ADJ alcohol) phenyl ADJ ethanol)) AND (@pd<"20030613" or @ad<"20030613" or @prad<"20030613" or @rlad<"20030613" or @ptad<"20030613") AND (nasal nose) AND (spray drop)	US-PGPUB; USPAT; USOCR	OR	ON	2011/09/06 17:12
S36	23	((microcrystalline NEAR3 cellulose) AND (carboxymethyl NEAR3 cellulose) AND ((phenyl ADJ ethyl ADJ alcohol) phenyl ADJ ethanol)) AND (@pd<"20030613" or @ad<"20030613" or @prad<"20030613" or @rlad<"20030613" or @ptad<"20030613") AND (antihistamine steroid) AND (nasal nose) AND (spray	US-PGPUB; USPAT; USOCR	OR	ON	2011/09/06 17:13

		drop)				
S37	1158	((microcrystalline NEAR3 cellulose) AND (carboxymethyl NEAR3 cellulose)) AND (@pd<"20030613" or @ad<"20030613" or @prad<"20030613" or @rlad<"20030613" or @ptad<"20030613") AND (antihistamine steroid) AND (nasal nose) AND (spray drop)	US-PGPUB; USPAT; USOCR	OR	ON	2011/09/06 17:26
S38	592	((microcrystalline NEAR3 cellulose) AND (carboxymethyl NEAR3 cellulose)) AND (@pd<"20030613" or @ad<"20030613" or @prad<"20030613" or @rlad<"20030613" or @ptad<"20030613") AND (antihistamine steroid) AND ((nasal nose) SAME (spray drop))	US-PGPUB; USPAT; USOCR	OR	ON	2011/09/06 17:26
S39	25	((microcrystalline NEAR3 cellulose) AND (carboxymethyl NEAR3 cellulose)) AND (@pd<"20030613" or @ad<"20030613" or @prad<"20030613" or @rlad<"20030613" or @ptad<"20030613") AND ((antihistamine steroid) SAME (nasal nose) SAME (spray drop))	US-PGPUB; USPAT; USOCR	OR	ON	2011/09/06 17:27
S40	13	((phenyl ADJ ethyl NEAR3 alcohol) (phenyl ADJ ethanol)) AND (@pd<"20030613" or @ad<"20030613" or @prad<"20030613" or @rlad<"20030613" or @ptad<"20030613") AND ((antihistamine steroid) SAME (nasal nose) SAME (spray drop))	US-PGPUB; USPAT; USOCR	OR	ON	2011/09/06 17:38
S41	2	(preservative SAME((phenyl ADJ ethyl NEAR3 alcohol) (phenyl ADJ ethanol))) AND (@pd<"20030613" or @ad<"20030613" or @prad<"20030613" or @rlad<"20030613" or @ptad<"20030613") AND ((antihistamine steroid) SAME (spray drop))	US-PGPUB; USPAT; USOCR	OR	ON	2011/09/06 17:41

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L2	1798	fluticasone	USPAT; UPAD	OR	ON	2011/09/14 09:55
L3	0	(514/171).CCLS.	UPAD	OR	OFF	2011/09/14 09:55

9/14/2011 11:39:51 AM
C:\Users\tnielsen\Documents\EAST\Workspaces\10518016.wsp

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

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Date: October 5, 2005

/Thor Nielsen/ 09/23/2011

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

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
		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	/Thor Nielsen/	DATE CONSIDERED	09/23/2011

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Issue Classification

Application/Control No.	Applicant(s)/Patent Under Reexamination
10518016	LULLA ET AL.
Examiner	**Art Unit**
THOR NIELSEN	1616

ORIGINAL	
CLASS	SUBCLASS
514	171

CROSS REFERENCE(S)

CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)				

INTERNATIONAL CLASSIFICATION																					
CLAIMED										NON-CLAIMED											
A	0	1	N	45 / 00 (2006.01.01)																	
A	6	1	K	31 / 56 (2006.01.01)																	
A	6	1	K	31 / 55 (2006.01.01)																	
A	6	1	K	31 / 57 (2006.01.01)																	
A	6	1	K	31 / 58 (2006.01.01)																	
A	6	1	K	9 / 00 (2006.01.01)																	
A	6	1	P	37 / 08 (2006.01.01)																	
A	6	1	P	27 / 14 (2006.01.01)																	
A	6	1	P	11 / 06 (2006.01.01)																	

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

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	1	-	17	-	33	-	49	34	65						
2	2	-	18	-	34	-	50	35	66						
-	3	12	19	17	35	-	51	36	67						
3	4	13	20	18	36	-	52	37	68						
-	5	14	21	19	37	22	53	38	69						
4	6	15	22	20	38	23	54	39	70						
5	7	-	23	-	39	24	55	40	71						
6	8	-	24	-	40	25	56	41	72						
-	9	-	25	-	41	26	57	42	73						
8	10	-	26	-	42	27	58	43	74						
-	11	-	27	-	43	28	59	44	75						
-	12	-	28	-	44	29	60	45	76						
9	13	-	29	21	45	30	61	46	77						
7	14	16	30	-	46	31	62	47	78						
10	15	-	31	-	47	32	63	48	79						
11	16	-	32	-	48	33	64								

/THOR NIELSEN/ Examiner.Art Unit 1616 (Assistant Examiner)	09/14/2011 (Date)	**Total Claims Allowed:** 48	
/JOHANN RICHTER/ Supervisory Patent Examiner.Art Unit 1616 (Primary Examiner)	09/15/2011 (Date)	O.G. Print Claim(s) 1, 21	O.G. Print Figure None

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (01-10)
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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	Thor B. Nielsen
Attorney Docket Number	PAC/20632 US (4137-04700)

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/Thor Nielsen/ 09/23/2011

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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	Thor B. Nielsen
	Attorney Docket Number	PAC/20632 US (4137-04700)

	1	SALIB RAMI JEAN, et al., "Safety and Tolerability Profiles of Intranasal Antihistamines and Intranasal Corticosteroids in the Treatment of Allergic Rhinitis," Drug Safety 2003, Vol. 26, No. 12, Cover page, publication page, pgs. 863-893, ADIS Data Information BV.	☐
	2	SIMPSON, RICHARD J., "Budesonide and terfenadine, separately and in combination, in the treatment of hay fever," Annals of Allergy, December, 1994, Vol. 73, Cover page, publication page, pgs. 497-502.	☐
	3	JUNIPER, E F., et al., "Comparison of beclomethasone dipropionate aqueous nasal spray, astemizone, and the combination in the prophylactic treatment of ragweed pollen-induced rhinoconjunctivitis," Journal of Allergy and Clinical Immunology, March 1989, Vol 83, No. 3, Cover page, Publications page, pgs. 627-633, American Academy of Allergy and Immunology, C.V. Mosby Co.	☐
	4	BARNES, M. L., et al., "Effects of levocetirizine as add-on therapy to fluticasone in seasonal allergic rhinitis," Clinical and Experimental Allergy, January 27, 2006, Vol. 36, pgs. 676-684, Blackwell Publishing Ltd.	☐
	5	Applicants response to foreign communication - EP 03738280.1 (EP Patent 1519731) , September 6, 2010, 15 pages.	☐
	6	File history of Australian Patent Application No. AU2003244799, 38 pages.	☐
	7	File history of Brazilian Patent Application No. PI 0312128-3, 27 pages.	☐
	8	File history of Canadian Patent Application No. 2,489,427, 19 pages.	☐
	9	File history of Korean Patent Application No. 10-2004-7020819, 89 pages.	☐
	10	File history of Mexican Patent Application No. PA/a/2004/01266 (now Patent No. 265349), 86 pages.	☐
	11	File history of Polish Patent Application No. P 373001, 95 pages.	☐

/Thor Nielsen/ 09/23/2011

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	Thor B. Nielsen
	Attorney Docket Number	PAC/20632 US (4137-04700)

	12	File history of Russian Patent Application No. RU 2361593 C2, 65 pages.	☐
	13	File history of South African Patent Application No. 2005/0331 (now Patent No. 2005/0331), 18 pages.	☐
	14	Applicants response to foreign communication - CA 2489427, December 20, 2010, 10 pages.	☐

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EXAMINER SIGNATURE

Examiner Signature	/Thor Nielsen/	Date Considered	09/23/2011

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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	Thor B. Nielsen
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

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☐ 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)	2011-08-16
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.**

/Thor Nielsen/ 09/23/2011

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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.

/Thor Nielsen/ 09/23/2011

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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**
514	171	09/14/2011	TBN

SEARCH NOTES		
Search Notes	**Date**	**Examiner**
East Search	11/4/2009	KB
East Search	11/6/2009	KB
EAST prior art search	09/14/2011	TBN

INTERFERENCE SEARCH			
Class	**Subclass**	**Date**	**Examiner**
514	171	09/14/2011	TBN

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	08/16/2011					
=	1	✓	✓	✓						
=	2	✓	✓	✓						
-	3	✓	✓	-						
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=	36	✓	✓	✓						

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CLAIM		DATE								
Final	Original	09/23/2008	01/21/2009	10/29/2009	08/16/2011					
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=	38	✓	✓	✓						
-	39	✓	✓	-						
-	40	✓	✓	-						
-	41	✓	✓	-						
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-	44	✓	✓	✓						
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-	48	N	N	-						
-	49	N	N	-						
-	50	N	N	-						
-	51		N	-						
-	52		N	-						
=	53			✓						
=	54			✓						
=	55			✓						
=	56			✓						

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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

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	First Named Inventor	Amar Lulla
	Art Unit	1616
	Examiner Name	Thor B. Nielsen
	Attorney Docket Number	PAC/20632 US(4137-04700)

	1	Applicant Response to foreign communication EP Patent 1519731, August 11, 2011, 252 pages.	☐

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Examiner Signature	/Thor Nielsen/	Date Considered	09/14/2011

*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.

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Art Unit	1616
Examiner Name	Thor B. Nielsen
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.

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

☐ A certification statement is not submitted herewith.

SIGNATURE

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

Signature	/Rodney B. Carroll/	Date (YYYY-MM-DD)	2011-08-22
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.**

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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).

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/Thor Nielsen/ 09/14/2011

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Doc description: Information Disclosure Statement (IDS) Filed

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

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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	5232919		1993-08-03	Scheffler, et al.	
	2	5271946		1993-12-21	Hettche	
	3	5658919		1997-08-19	Ratnaraj, et al.	
	4	6319513	B1	2001-11-20	Dobrozsi	
	5	7776315	B2	2010-08-17	Pairet, et al.	
	6	5914122		1999-06-22	Otterbeck, et al.	
	7	6525228	B2	2003-02-25	Chauvin, et al.	

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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	20040204399	A1	2004-10-14	Osbakken, et al.	
	2	20040235807	A1	2004-11-25	Weinrich, et al.	

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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	10152369	DE	A1	2002-05-08	Boehringer Ingelheim Pharma		☐
	2	9746243	WO	A1	1997-12-11	The Procter & Gamble Company		☐
	3	2003244799	AU	B2	2003-12-31	Cipla Limited		☐
	4	2002-053485	JP		2002-02-19	Oshida Tetsuo		☐

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	1	Foreign communication from a related counterpart application - CA2,489,427, Examination Report, June 18, 2010, 3 pages.	☐
	2	Foreign communication from a related counterpart application - CA2,489,427, Examination Report, March 24, 2011, 2 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	Foreign communication from a related counterpart application - Notice of Intent to Grant, EP Application 03738280.1, October 23, 2008, 6 pages.	☐
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	8	GENNARO, ALFONSO R., ed., et al., Remington: The Science and Practice of Pharmacy, 2000, 20th edition, Vol. 1, pgs. 785, 830, 831 plus cover page and publication page, Lippincott Williams & Wilkins.	☐
	9	GILBERT, PETER, et al., "Preservation of pharmaceutical products," Encyclopedia of Pharmaceutical Technology, 2002, 2nd edition, Vol. 3, pg. 2278 plus cover page and publication page, Marcel Dekker, Inc.	☐
	10	Office Action (Final) dated February 18, 2011 (23 pages), Application Serial No. 12/508,388 filed on July 23, 2009.	☐
	11	Office Action (Final) dated February 24, 2011 (20 pages), Application Serial No. 12/508,393 filed July 23, 2009.	☐
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	12	REDDY, INDRA K., ed., Ocular Therapeutics and Drug Delivery: A Multi-Disciplinary Approach, 1996, pgs. 382-385 plus cover page and publication page, Technomic Publishing Company, Inc.	☐
	13	Foreign communication from a related counterpart application - Summons to Attend Oral Proceedings, EP Application 03738280.1, February 8, 2011, 1 page.	☐
	14	Foreign communication from a related counterpart application - Examination Report, RU 2005100781, April 23, 2007, 6 pages.	☐
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	16	Pre-Grant Opposition, Indian Patent Application 2092/KOLNP/2007 dated June 8, 2007, 183 pages.	☐
	17	SPECTOR, SHELDON, "Ideal pharmacotherapy for allergic rhinitis," J Allergy Clin Immunol, Vol. 103, No. 3, Part 2, pgs. S386-S387. 1999	☐
	18	MCNEELY, WENDY, et al., "Intranasal Azelastine A Review of its Efficacy in the Management of Allergic Rhinitis," Drugs, 1998, Vol. 56, No. 1, pgs. 91-114.	☐
	19	ABPI Data Sheet Compendium, 1995-96, cover page plus pgs. 38-39, Datapharm Publications Limited, London, Great Britain.	☐
	20	AURORA, JACK, "Nasal Delivery; Development of Nasal Delivery Systems: A Review," Drug Delivery Technology, Vol. 2, No. 7, October 2002, 8 pages, http://www.drugdeliverytech.com/ME2/Segments/Publications: Article&id=9EB19EB2F29F462089CE081473F5F3CA.	☐
	21	BLOCK, JOHN H., et al., "Inorganic Medicinal and Pharmaceutical Chemistry," 1986, cover, publication, and preface pages plus page 100, Indian Edition, Varghese Publishing House, Bombay, India.	☐
	22	Cipla Sixty-Ninth Annual Report 2004-2005, cover pages, information page, plus pgs. 3, 5, and 44.	☐

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	23	Duonase Data Sheet, "The Complete Rhinitis Control," 6 pages, Cipla Limited, Mumbai, India. 2004	☐
	24	DROUIN, MICHEL A., et al., "Adding Loratadine to Topical Nasal Steroid Therapy Improves Moderately Severe Seasonal Allergic Rhinoconjunctivitis," Advances in Therapy, Vol. 12, No. 6, November/December 1995, pgs. 340 - 349, Health Communications Inc.	☐
	25	Foreign communication from a related counterpart application - Translation of Office Action, Israel Patent Application 165771, July 11, 2011, 3 pages.	☐
	26	HODGES, N. A., et al., "Preservative Efficacy Tests in Formulated Nasal Products: Reproducibility and Factors Affecting Preservative Activity," J. Pharm. Pharmacol., 1996, Vol. 48, pgs. 1237-1242.	☐
	27	Applicants response to foreign communication - KR10-2004-7020819, December 27, 2010, 18 pages.	☐
	28	Prescribing Information for Astepro®, November 2010, 20 pages, Meda Pharmaceuticals Inc., Somerset, NJ, US.	☐
	29	Prescribing Information for Rhinocort Aqua™, December 2010, 32 pages, AstraZeneca LP, Wilmington, DE, US.	☐
	30	Product Information, Nasonex®, August 2001, 22 pages, Schering Corporation, Kenilworth, NJ, US.	☐
	31	Safety Data Sheet, SDS Number 110556, July 4, 2008, V14, Flonase Nasal Spray, 5 pages, GlaxoSmithKline.	☐
	32	Safety Data Sheet, SDS Number 110536, June 23, 2008, V13, Beconase Hayfever Allergy Spray, 5 pages, GlaxoSmithKline.	☐
	33	WISEMAN, LYNDA R., et al., "Intranasal Fluticasone Propionate: A Reappraisal of its Pharmacology and Clinical Efficacy in the Treatment of Rhinitis," Drugs, 1997, Vol. 53, No. 5, pgs. 885-907, Adis International Limited.	☐
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	34	World Review 2001: The Pharmaceutical Market, Vol. 1 International, IMS Health, 2001, cover, preface, and copyright pages plus pages 4-42 and 5-1 through 5-11, IMS A.G.	☐
	35	Opposition to EP 1518731, August 8, 2011, 19 pages.	☐
	36	BERGE, STEPHEN M., et al., "Pharmaceutical Salts," Journal of Pharmaceutical Sciences, Vol. 66, No. 1, January 1977, pgs. 1-19.	☐
	37	Product Specification Bulletin, Avicel® RC-591, Bulletin AVC591-SPEC-02/09.RS, 2 pages, FMC BioPolymer. Feb. 2009	☐
	38	Product Specification Bulletin, Avicel® CL-611, Bulletin AVC611-SPEC-02/09.RS, 2 pages, FMC BioPolymer. Feb. 2009	☐
	39	Avicel® RC/CL, Microcrystalline Cellulose And Carboxymethylcellulose Sodium, NF Dispersible Cellulose, BP, Specifications and Analytical Methods, RC-16 Updated 10/95 (2/99), 6 pages, FMC BioPolymer.	☐
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	First Named Inventor	Amar Lulla
	Art Unit	1616
	Examiner Name	Thor B. Nielsen
	Attorney Docket Number	PAC/20632 US (4137-04700)

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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.

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	2	SIMPSON, RICHARD J., "Budesonide and terfenadine, separately and in combination, in the treatment of hay fever," Annals of Allergy, December, 1994, Vol. 73, Cover page, publication page, pgs. 497-502.	☐
	3	JUNIPER, E F., et al., "Comparison of beclomethasone dipropionate aqueous nasal spray, astemizone, and the combination in the prophylactic treatment of ragweed pollen-induced rhinoconjunctivitis," Journal of Allergy and Clinical Immunology, March 1989, Vol 83, No. 3, Cover page, Publications page, pgs. 627-633, American Academy of Allergy and Immunology, C.V. Mosby Co.	☐
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	5	Applicants response to foreign communication - EP 03738280.1 (EP Patent 1519731) , September 6, 2010, 15 pages.	☐
	6	File history of Australian Patent Application No. AU2003244799, 38 pages.	☐
	7	File history of Brazilian Patent Application No. PI 0312128-3, 27 pages. April 2011	☐
	8	File history of Canadian Patent Application No. 2,489,427, 19 pages. December 2010	☐
	9	File history of Korean Patent Application No. 10-2004-7020819, 89 pages.	☐
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	12	File history of Russian Patent Application No. RU 2361593 C2, 65 pages. April 2009	☐
	13	File history of South African Patent Application No. 2005/0331 (now Patent No. 2005/0331), 18 pages.	☐
	14	Applicants response to foreign communication - CA 2489427, December 20, 2010, 10 pages.	☐

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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.

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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.

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

/Thor Nielsen/ 08/28/2011

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	Thor B. Nielsen
Attorney Docket Number	PAC/20632 US(4137-04700)

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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	Thor B. Nielsen
	Attorney Docket Number	PAC/20632 US(4137-04700)

	1	Applicant Response to foreign communication EP Patent 1519731, August 11, 2011, 252 pages.	☐

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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	Thor B. Nielsen
	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.

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

☐ A certification statement is not submitted herewith.

SIGNATURE

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

Signature	/Rodney B. Carroll/	Date (YYYY-MM-DD)	2011-08-22
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.**

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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:	10787212
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-AUG-2011
Filing Date:	06-JUL-2005
Time Stamp:	18:06:32
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	5253
Deposit Account	501515
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		00216.pdf			

1	Information Disclosure Statement (IDS) Form (SB08)	082211_IDS.pdf	753941 375c0d1dcbec6f803bb37f7fa2a815df8870d0ef	no	4

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2	Non Patent Literature	081111_Applicant_Response_To_Oral_Summons.pdf	18321905 478c89534c3e7ee73668aef2c61073be81955611	no	252

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<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.

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<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.

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: Thor B. Nielsen
§
§ 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 8/16/11

Edith Shek

Edith Shek

AMENDMENTS AND RESPONSE TO OFFICE ACTION DATED FEBRUARY 16, 2011

Dear Sir:

In response to the Office Action dated February 16, 2011, Applicants respectfully request reconsideration of the above-identified application as follows.

Amendment to the Specification begins on page 2 of this paper

Amendments to the Claims are reflected in the listing of claims, which begins on page 4 of this paper.

Remarks/Arguments begin on page 15 of this paper.

Supplemental IDS is submitted herewith.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Amar Lulla, *et al.*

Serial No.: 10/518,016

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Remarks/Arguments begin on page 15 of this paper.

Supplemental IDS is submitted herewith.

AMENDMENTS TO THE SPECIFICATION

(1) Please replace paragraph **[0007]** of the US Patent Application Publication No. US 2006/0025391 A1 in its entirety with the following paragraph:

[0007] 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. In an embodiment, the formulation contains the steroid in an amount from about 50 micrograms/ml to about 5 mg/ml of the formulation. In an embodiment, the formulation contains a suspension containing 0.0005% to 2% (weight/weight of the formulation) of azelastine or a pharmaceutically acceptable salt of azelastine, and from 0.0357% (weight/weight of the formulation), alternatively from 0.5%, to 1.5% (weight/weight of the formulation) of said steroid. In an embodiment, the formulation contains a suspension containing from 0.001% to 1% (weight/weight of the formulation) azelastine, or salt thereof, and from 0.0357% (weight/weight of the formulation), alternatively from 0.5%, to 1.5% (weight/weight of the formulation) steroid.

(2) Please replace paragraph **[0023]** of the US Patent Application Publication No. US 2006/0025391 A1 in its entirety with the following paragraph:

[0023] In the event of the use of Avicel RC 591 or [[CL11]]CL 611, microcrystalline cellulose and carboxymethyl cellulose sodium commercially available from FMC BioPolymer, 0.65-3.0% by weight of the formulation, for example, is used for the purpose.

(3) Please replace paragraph **[0036]** of the US Patent Application Publication No. US 2006/0025391 A1 in its entirety with the following paragraph:

[0036] 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. In an embodiment, the formulation contains from about 50 micrograms to about 1 milligram of surfactant per ml of the formulation.

AMENDMENTS TO THE CLAIMS

Listing of claims:

1. (Currently Amended) A pharmaceutical formulation ~~which comprises~~comprising:

azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, and

~~fluticasone or~~ a pharmaceutically acceptable ester ~~thereof~~of fluticasone,

wherein said pharmaceutical formulation is in a dosage form suitable for nasal administration. ~~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. (Currently Amended) [[A]]The pharmaceutical formulation ~~according to~~ of claim 1, wherein said pharmaceutically acceptable salt of azelastine is ~~present as~~ azelastine hydrochloride.

3. (Canceled)

4. (Currently Amended) [[A]]The pharmaceutical formulation ~~according to~~ of claim 1, wherein [[the]]said pharmaceutically acceptable ester of fluticasone is fluticasone propionate or fluticasone valerate.

5. (Canceled)

6. (Currently Amended) [[A]]The pharmaceutical formulation ~~according to~~ of claim 1, wherein [[the]]said formulation has a particle size of less than 10 μm.

7. (Currently Amended) [[A]]The pharmaceutical formulation ~~according to~~ of 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~~ wherein said formulation is an aqueous suspension comprising from 0.0005% (weight/weight) to 2% (weight/weight) of said azelastine, or said pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, and from 0.0357% (weight/weight) to 1.5% (weight/weight) of said pharmaceutically acceptable ester of fluticasone.

8. (Currently Amended) [[A]]The pharmaceutical formulation according to claim 7, ~~which contains~~ comprising from 0.001% (weight/weight) to 1% (weight/weight ~~of the formulation~~) of said azelastine, or said pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, and from [[0.5]]0.0357% (weight/weight) to 1.5% (weight/weight ~~of the formulation~~) ~~fluticasone or a~~of said pharmaceutically acceptable ester ~~thereof~~of fluticasone.

9. (Canceled)

10. (Currently Amended) [[A]]The pharmaceutical formulation ~~according to claim 9~~ of claim 14, wherein [[the]]said surfactant comprises a polysorbate, [[or]]poloxamer ~~surfactant~~ or combinations thereof.

11-12. (Canceled)

13. (Currently Amended) [[A]]The pharmaceutical formulation ~~according to claim 12~~ of claim 14, wherein [[the]]said isotonic agent comprises sodium chloride, saccharose, glucose, glycerine, sorbitol, [[or]]1,2-propylene glycol or combinations thereof.

14. (Currently Amended) [[A]]The pharmaceutical formulation ~~according to~~ of claim 1, ~~which also contains~~ further comprising at least one additive selected from the group consisting of a buffer, a preservative, a suspending agent, [[and]]a thickening agent, a surfactant, an isotonic agent and combinations thereof.

15. (Currently Amended) [[A]]The pharmaceutical formulation ~~according to~~ of claim 14, wherein said preservative ~~is selected from~~ comprises edetic acid [[and]]or its alkali salts, lower alkyl p-hydroxybenzoates, chlorhexidine, phenyl mercury borate, or benzoic acid or a salt thereof, a quaternary ammonium compound, [[or]]sorbic acid or a salt thereof, or combinations thereof.

16. (Currently Amended) [[A]]The pharmaceutical formulation ~~according to~~ of claim 14, wherein [[the]]said suspending agent or said thickening agent ~~is selected from~~ comprises 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, or combinations thereof.

17-18. (Canceled)

19. (Currently Amended) [[A]]The pharmaceutical formulation ~~according to~~ of claim 1, which is an aqueous suspension ~~or solution~~.

20. (Currently Amended) [[A]]The pharmaceutical formulation ~~according to~~ of 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~~wherein said dosage form suitable for nasal administration comprises nasal drops or a nasal spray.

21. (Currently Amended) [[A]]The pharmaceutical formulation ~~according to claim 20~~of claim 1, ~~which is in the form of~~ wherein said dosage form suitable for nasal administration comprises nasal drops ~~or nasal spray~~.

22. (Currently Amended) [[A]]The pharmaceutical formulation ~~according to claim 20~~of claim 1, ~~which is in the form of an aerosol~~ wherein said dosage form suitable for nasal administration comprises a nasal spray.

23-29. (Canceled)

30. (Currently Amended) [[A]]The pharmaceutical ~~product comprising the~~ formulation ~~according to~~ of 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 use~~ said formulation is used 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]]The ~~pharmaceutical product comprising the~~ pharmaceutical formulation of claim 1, wherein said pharmaceutically acceptable salt of azelastine is azelastine hydrochloride and said pharmaceutically acceptable ester of fluticasone is fluticasone propionate, ~~as a combined preparation for simultaneous, separate or sequential use~~ and wherein said formulation is used 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]]The pharmaceutical formulation ~~according to~~ of claim 1, wherein said pharmaceutically acceptable salt of azelastine is azelastine hydrochloride and said pharmaceutically acceptable ester of fluticasone is fluticasone propionate, ~~together with~~ and wherein said formulation further comprises a pharmaceutically acceptable carrier or excipient therefor.

37. (Currently Amended) [[A]]The ~~pharmaceutical product comprising the~~ pharmaceutical formulation of claim 1, wherein said pharmaceutically acceptable salt of azelastine is azelastine hydrochloride and said pharmaceutically acceptable ester of fluticasone is fluticasone valerate, ~~as a combined preparation for simultaneous, separate or sequential use~~ and wherein said formulation is

used 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]]The pharmaceutical formulation ~~according to~~ of claim 1, wherein said pharmaceutically acceptable salt of azelastine is azelastine hydrochloride and said pharmaceutically acceptable ester of fluticasone is fluticasone valerate, ~~together with~~ and wherein said formulation further comprises a pharmaceutically acceptable carrier or excipient therefor.

39-44. (Canceled)

45. (Currently Amended) A process of preparing a pharmaceutical formulation ~~according to~~ of 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~~of fluticasone.

46-52. (Canceled)

53. (Currently Amended) [[A]]The pharmaceutical formulation ~~according to~~ of claim 1, wherein [[the]]said pharmaceutically acceptable ester of fluticasone is fluticasone propionate.

54. (Currently Amended) [[A]]The pharmaceutical formulation ~~according to~~ of claim 1, wherein [[the]]said pharmaceutically acceptable ester of fluticasone is fluticasone valerate.

55. (Currently Amended) A pharmaceutical ~~product~~ formulation comprising [[(i)]] azelastine hydrochloride; and,

fluticasone propionate,

wherein said formulation is in the dosage form of ~~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~~ wherein said formulation is used in the treatment of conditions for which administration of one or more anti-histamine and/or one or more steroid is indicated.

56. (Currently Amended) 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~~of fluticasone, ~~together with~~ and (iii) a pharmaceutically acceptable carrier or excipient therefor.

57. (New) The pharmaceutical formulation of claim 8, comprising 0.1% (weight/weight) of azelastine hydrochloride, and from 0.0357% to 1.5% (weight/weight) of fluticasone propionate.

58. (New) The pharmaceutical formulation of claim 8, comprising 0.1% (weight/weight) of azelastine hydrochloride, and from 0.0357% to 1.5% (weight/weight) of fluticasone valerate.

59. (New) The pharmaceutical formulation of claim 8, wherein said dosage form suitable for nasal administration comprises a nasal spray.

60. (New) The pharmaceutical formulation of claim 57, wherein said dosage form suitable for nasal administration comprises a nasal spray.

61. (New) The pharmaceutical formulation of claim 58, wherein said dosage form suitable for nasal administration comprises a nasal spray.

62. (New) The pharmaceutical formulation of claim 59, wherein said pharmaceutically acceptable salt of azelastine is azelastine hydrochloride and wherein said pharmaceutically acceptable ester of fluticasone is fluticasone propionate.

63. (New) The pharmaceutical formulation of claim 59, wherein said pharmaceutically acceptable salt of azelastine is azelastine hydrochloride and wherein said pharmaceutically acceptable ester of fluticasone is fluticasone valerate.

64. (New) The pharmaceutical formulation of claim 60, wherein said pharmaceutically acceptable salt of azelastine is azelastine hydrochloride and wherein said pharmaceutically acceptable ester of fluticasone is fluticasone propionate.

65. (New) The pharmaceutical formulation of claim 61, wherein said pharmaceutically acceptable salt of azelastine is azelastine hydrochloride and wherein said pharmaceutically acceptable ester of fluticasone is fluticasone valerate.

66. (New) The pharmaceutical formulation of claim 7, wherein said pharmaceutically acceptable salt of azelastine is azelastine hydrochloride.

67. (New) The pharmaceutical formulation of claim 8, wherein said pharmaceutically acceptable salt of azelastine is azelastine hydrochloride.

68. (New) The pharmaceutical formulation of claim 59, wherein said pharmaceutically acceptable salt of azelastine is azelastine hydrochloride.

69. (New) The pharmaceutical formulation of claim 10, wherein said surfactant comprises a polysorbate.

70. (New) The pharmaceutical formulation of claim 13, wherein said isotonic agent comprises glycerine.

71. (New) The pharmaceutical formulation of claim 15, wherein said preservative comprises edetate disodium and benzalkonium chloride.

72. (New) The pharmaceutical formulation of claim 16, wherein said suspending agent or said thickening agent comprises cellulose derivatives.

73. (New) The pharmaceutical formulation of claim 1, further comprising edetate disodium, glycerine, a thickening agent comprising microcrystalline cellulose and sodium carboxy methyl cellulose, polysorbate 80, benzalkonium chloride, phenyl ethyl alcohol, and purified water.

74. (New) The pharmaceutical formulation of claim 55, further comprising edetate disodium, glycerine, a thickening agent comprising microcrystalline cellulose and sodium carboxy methyl cellulose, polysorbate 80, benzalkonium chloride, phenyl ethyl alcohol, and purified water.

75. (New) The pharmaceutical formulation of claim 56, further comprising edetate disodium, glycerine, a thickening agent comprising microcrystalline cellulose and sodium carboxy methyl cellulose, polysorbate 80, benzalkonium chloride, phenyl ethyl alcohol, and purified water.

76. (New) The pharmaceutical formulation of claim 1, wherein said formulation comprises a pH from 3 to 7.

77. (New) The pharmaceutical formulation of claim 1, wherein said formulation comprises a pH from 4.5 to 6.5.

78. (New) A pharmaceutical formulation comprising from 0.001% (weight/weight) to 1% (weight/weight) of azelastine hydrochloride, and from 0.0357% (weight/weight) to 1.5% (weight/weight) of fluticasone propionate, wherein said pharmaceutical formulation is an aqueous suspension suitable for nasal administration.

79. (New) A pharmaceutical formulation comprising 1% (weight/weight) of azelastine hydrochloride, and from 0.0357% (weight/weight) to 1.5% (weight/weight) of fluticasone propionate, wherein said pharmaceutical formulation is an aqueous suspension suitable for nasal administration.

REMARKS/ARGUMENTS

Status of Claims

Claims 1-2, 4, 6-8, 10, 13-16, 19-22, 30, 35-38, 45, and 53-56 have been amended.

Claims 3, 5, 9, 11-12, 17-18, 23-29, 31-34, 39-44, and 46-52 have been canceled.

Claims 57-79 are new.

Thus, claims 1-2, 4, 6-8, 10, 13-16, 19-22, 30, 35-38, 45, and 53-79 are currently pending in this application.

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

Amendments to Specification

Applicants have amended paragraph [0007] of the US Patent Application Publication No. US 2006/002539 A1. Support for the amendment is found in claims 5, 7 and 8 of the priority International Application No. PCT/GB2003/02557 (International Publication No. WO 2003/105856). Also, support for the "0.0357" endpoint is provided in Examples 3 and 4 of the specification.

Applicants have amended paragraph [0023] of the US Patent Application Publication No. US 2006/002539 A1 to correct an obvious typographical error in the designation of Avicel CL 611 and to provide a generic description of the trademarked product. Support for the amendment is provided in Example 7 of the specification and in the manufacturer's product sheets for Avicel RC 591 and CL 611 provided herewith as Exhibits I, II, and III.

Applicants have amended paragraph [0036] of the US Patent Application Publication No. US 2006/002539 A1. Support for the amendment is found in claim 11 of the priority

International Application No. PCT/GB2003/02557 (International Publication No. WO 2003/105856).

Applicants respectfully submit each of the above amendments is supported by the application as originally filed and that no new matter is introduced by way of these amendments.

Amendments to the Claims

The pending dependent claims have been amended to correspond in scope and terminology to the substantive amendments to independent claims 1, 55, and 56, discussed in more detail below. Additionally, claims 7 and 8 have been amended to recite a lower endpoint of "0.0357%" for the pharmaceutically acceptable ester of fluticasone, which is supported at least by Examples 3 and 4.

New claims 57-79 recite novel and non-obvious aspects of the invention not disclosed by the prior art of record. The new claims are supported by at least the following (referring to paragraph numbers from the published U.S. Application): claims 57, 59, 60, 62, and 64 are supported by Example 3; claims 58, 61, 63, and 65 are supported by Example 4; claims 66, 67, and 68 are supported by paragraphs 0050 and 0051; claims 69-75 are supported by Examples 1, 3, and 4; claims 76-77 are supported by paragraph 24; and claims 78-79 are supported by Examples 1 and 3 and original claim 8.

The new claims 57-77 each depend from an independent claim, and therefore are allowable over the prior art of record for the reasons set forth below. New independent claims 78 and 79, having limitations similar to the other independent claims, are each allowable for the same reasons discussed in detail below.

Applicants respectfully submit each of the above amendments is supported by the application as originally filed and that no new matter is introduced by way of these amendments.

Examiner Interview

Applicants thank the Examiner for the courtesy of a telephonic interview on August 1, 2011, the substance of which is accurately reflected in the Interview Summary mailed August 4, 2011.

Previous Submissions

In response to the remarks set forth on page 10, paragraph 2 of the February 16, 2011 Office Action regarding the second §1.132 Declaration of Geena Malhotra dated September 23, 2010 (the "*Malhotra II Declaration*") and submitted with the September 24, 2010 Response to Office Action, and without conceding any deficiencies, Applicants respectfully submit that the stability testing set forth in the *Malhotra II Declaration* complies with the standards set forth in the ICH guideline Q1A(R2), Stability Testing of New Drug Substances and Products, attached hereto as Exhibit IV.

Furthermore, Applicants respectfully affirm, incorporate by reference herein, and reserve for purposes of appeal the various arguments for patentability set forth in the previous Responses to Office Action. Accordingly, the following remarks are focused on the new claim amendments and supporting declaratory evidence provided herewith.

Claim Rejections – 35 U.S.C. § 102

Claims 1-2, 9-10, 12-21, 30, 45 and 55-56 stand rejected as anticipated by EP 0780127 ("*Cramer*"). Independent claims 1 and 56 have been amended to recite "a pharmaceutically acceptable ester of fluticasone," and claim 55 has been amended to recite "fluticasone propionate." New independent claims 78 and 79 likewise recite "fluticasone propionate." *Cramer* does not disclose the claimed pharmaceutically acceptable esters of fluticasone. Rather, *Cramer* discloses on page 3, lines 15-18:

> 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.

Thus, at most *Cramer* discloses, among other glucocorticoid agents, fluticasone and pharmaceutically acceptable salts thereof. *Cramer* does not disclose "a pharmaceutically acceptable ester of fluticasone" as recited in the amended claims. Applicants respectfully submit that the lack of teaching in *Cramer* regarding "a pharmaceutically acceptable ester of fluticasone" is further evidenced by the rejection of dependent claim 4, reciting "fluticasone propionate or fluticasone valerate," under 35 U.S.C. §103 obviousness rather than §102 anticipation. That is, the Office Action has acknowledged that the specific esters recited in dependent claim 4 are not disclosed in *Cramer*, and thus are novel in view of *Cramer*. Thus, claims 55, 78, and 79 reciting "fluticasone propionate," as well as claims 1 and 56 reciting "a pharmaceutically acceptable ester of fluticasone" are novel. Accordingly, Applicants respectfully submit that amended independent claims 1, 55, 56, 78, and 79, as well as claims 2, 9-10, 12-21, 30, 45 (and all other claims) depending therefrom, are novel over *Cramer* and that the §102 rejection has been overcome.

Further, claim 1 has been amended to recite "said pharmaceutical formulation is in a dosage form suitable for nasal administration." Likewise, independent claims 55 and 56 each recite a "nasal spray," and new independent claims 78 and 79 each recite an "aqueous suspension suitable for nasal administration." On page 5, the Office Action notes that:

> "Cramer discloses the **preparation** of nasal sprays. See Examples." (emphasis in original)

As will be discussed in more detail below, Applicants have provided herewith a declaration establishing that Example 3 of *Cramer* (identified by the April 28, 2010 Office Action, page 16, as the closest example) is inoperable and unacceptable as a pharmaceutical formulation in a

dosage form suitable for nasal administration. In order to be anticipating, a prior art reference must be enabling so that the claimed subject matter may be made or used by one skilled in the art. *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1354 (Fed. Cir. 2003) ("Long ago our predecessor court recognized that a non-enabled disclosure cannot be anticipatory (because it is not truly prior art) if that disclosure fails to 'enable one of skill in the art to reduce the disclosed invention to practice.'" citing *In re Borst*, 52 C.C.P.A. 1398, 345 F.2d 851 (C.C.P.A. 1962)). Accordingly, the inoperability of *Cramer*'s closest example as cited by the Office Action is a further basis for the novelty of independent claims 1, 55, 56, 78, and 79 over *Cramer*, as well as claims 2, 9-10, 12-21, 30, 45 (and all other claims) depending therefrom.

Lastly, claim 1 has been amended to remove the language of previous dependent claim 5 directed to "fluticasone or a pharmaceutically acceptable ester thereof in an amount from about 50 micrograms/ml to about 5 mg/ml of the formulation," which was added to overcome the previous §102 anticipation rejection (subsequently reinstated by the present Examiner) and is now moot in view of the amendments set forth above.

Claim Rejections – 35 U.S.C. § 103

Claims 4, 7, 8, 11, 35, 36, 37, 38, 53, and 54 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over *Cramer.*

Claims 22, 26-27, and 44 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*").

Accordingly, the various §103 claim rejections are premised upon the application of the primary reference, *Cramer*, alone or in combination one of the secondary references, *Modi* or *Fassberg*.

A. Inoperability of *Cramer* Example 3 precludes a *prima facie* case of obviousness

In order to establish a *prima facie* case of obviousness, the Office Action must establish that the prior art teaches each and every element of the claimed invention, that the basis for any modification and/or combination of the prior art be clearly articulated, and that such modification and/or combination has a reasonable expectation of success. *See Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 22 (U.S. 1966) (an obviousness determination begins with a finding that "the prior art as a whole in one form or another contains all" of the elements of the claimed invention); *KSR Int'l Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 1741 (2007) ("'[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.'" (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006))); *Life Technologies Inc. v. Clontech Laboratories Inc.*, 224 F3d 1320, 56 USPQ2d 1186, 1190 (Fed.Cir. 2000) ("[f]or the [prior art] to render the claimed invention obvious, there must have been, at the time the invention was made, a reasonable expectation of success in applying [the prior art's] teachings."). Applicants respectfully submit the pending claims are patentable over the cited references because the Office Action fails to establish a *prima facie* case of obviousness in that *Cramer*, either alone or in combination, does not contain all the elements of the pending claims and the ordinarily skilled artisan would not have a reasonable expectation of success in modifying and/or combining *Cramer* given the inoperability thereof.

1. *Cramer* does not teach each and every element of the claimed invention

As noted above, each of the §103 rejections is premised upon the Office Action's application of *Cramer* as the primary reference. Furthermore, the April 28, 2010 Office Action at page 16 identified Example 3 of *Cramer* as the closest prior art example, and Applicants' previous §1.132 declaration was alleged to be deficient for failure to test against Example 3 of *Cramer*. While not admitting any previous deficiency, in an effort to substantively advance prosecution Applicants provide herewith the §1.132 Declaration of Geena Malhotra (the "*Malhotra III Declaration*") regarding Example 3 of *Cramer*. As set forth in the *Malhotra III Declaration*, Example 3 of *Cramer* was reproduced as described therein, and the formulation described in Example 3 of *Cramer* was found to be inoperable and unacceptable as a pharmaceutical formulation in a dosage form suitable for nasal administration. Specifically, as set forth in paragraph 9 of the *Malhotra III Declaration*:

> 9. From the observations set forth in paragraph 8, it is conclusive that the formulation described in Example 3 of *Cramer* is inoperable and unacceptable as a pharmaceutical formulation in a dosage form suitable for nasal administration for at least the following reasons:
>
> (A) Unacceptable settling and difficulty in resuspending – homogeneity of the active material in product is not expected to be maintained due to caking seen at the bottom of vial of the formulation;
>
> (B) Unacceptable jet rather than desired spray mist – after actuation of the nasal pump, the product comes out as jet (a stream of liquid forcefully shooting forth from the orifice) and not a spray (a mist of fine liquid particles), and due to which the drug is not expected to be suitably deposited on nasal mucosa; and
>
> (C) Unacceptable osmolality – It is widely known and accepted that nasal sprays are preferably isotonic (as is acknowledged by *Cramer* at page 3, lines 8 and 49) rather than hypertonic. Accordingly, the undesirable hyperosmotic (i.e., 554 mOsm/kg), hypertonic character of the product is expected to give rise to irritation of the nasal mucosa.

These experimental findings clearly establish that *Cramer's* Example 3 simply does not work as a nasal spray. A reference that lacks an enabling disclosure "may qualify as a prior art reference under §103, **but only for what is disclosed in it**." *Reading & Bates Constr. Co. v. Baker Energy*

Resources Corp., 748 F.2d 645, 652, 223 USPQ 1168, 1173 (Fed.Cir. 1985) (emphasis added). Thus, while Example 3 of *Cramer* may persist as prior art for purposes of an obviousness analysis despite the demonstrated inoperability thereof, Example 3 can be cited ***only for what is disclosed in it*** – critically, a non-working, rather than working, example. Therefore, for at least the reasons noted above, *Cramer*'s Example 3 does not disclose a pharmaceutical composition in a dosage form suitable for nasal administration and, as such, cannot be cited as teaching the same. Accordingly, because *Cramer* does not teach or suggest a pharmaceutical formulation in a dosage form suitable for nasal administration as recited in the amended claims, *Cramer* does not teach each and every element as required for a proper *prima facie* case of obviousness. Accordingly, the Office Action has failed to establish a *prima facie* case of obviousness as to the pending claims.

2. The secondary references, *Modi* and *Fassberg*, do not cure the deficiencies of the primary reference, *Cramer*

In view of acknowledged shortcomings of *Cramer*, the Office Action relies upon *Modi* for teaching aerosol sprays and metered dose inhalers (see February 16, 2011 Office Action, page 7) and upon *Fassberg* for teaching a particle size less than 10 μm (see April 28, 2010 Office Action, page 10). Thus, neither of the secondary references is relied upon to cure the major deficiencies outlined above for the primary reference, *Cramer*. Accordingly (and without conceding the propriety of such combinations), neither the combination of *Cramer* and *Modi* nor *Cramer* and *Fassberg* establish a *prima facie* case of obviousness as to the pending claims because such combinations do not teach each and every element of the pending claims. Accordingly, the Office Action has failed to establish a *prima facie* case of obviousness as to the pending claims.

3. The inoperability of *Cramer* precludes a reasonable expectation of success and teaches away

Furthermore, the inoperability of *Cramer*'s Example 3 (which was deemed to be the closest prior art example) would discourage a person skilled in the art from further experimentation, and therefore would teach away from any further modifications to *Cramer* or from combining *Cramer* with a secondary reference. "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant . . . [or] **if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant**." *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994) (emphasis added). "References that teach away cannot serve to create a *prima facie* case of obviousness." *See McGinley v. Franklin Sports*, 262 F.3d 1339, 1354 (Fed. Cir. 2001). Given that the pending claims are directed to formulations suitable for nasal administration and *Cramer's* Example 3 is demonstrably unsuitable for such use, a person skilled in the art would be discouraged from following the path set forth in Cramer's Example 3 as such is unlikely to be productive of the result sought by Applicants. Accordingly, a *prima facie* case of obviousness cannot be established on the basis of the prior art of record as the inoperability of *Cramer* precludes any reasonable expectation of success and teaches away from any further modifications and/or combinations with *Cramer*. Accordingly, the Office Action has failed to establish a *prima facie* case of obviousness as to the pending claims.

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

Even assuming *arguendo* the Office Action established a *prima facie* case of obviousness, which as demonstrated above it clearly has not, the following evidence of secondary considerations submitted herewith establishes that the pending claims are not obvious in view of the prior art of record. Under *Graham*, objective evidence of nonobviousness includes "commercial success, long-felt but unresolved needs, failure of others, copying, and unexpected results." *Ruiz v. AB Chance Co.*, 234 F. 3d 654, 663 (Fed. Cir. 2000). As evidence of such secondary considerations, Applicants provide the following declarations under 37 C.F.R. §1.132: (1) Declaration of Dr. Sujeet Rajan (the "*Rajan Declaration*") directed to the long felt need for the claimed pharmaceutical formulation; (2) Declaration of Dr. Joachim Maus (the "*Maus Declaration*") directed to the unexpected, beneficial results from clinical studies of the claimed pharmaceutical formulation; and (3) Declaration of Mr. Nikhil Chopra (the "*Chopra Declaration*") directed to the commercial success of the claimed pharmaceutical formulation. As described in detail below, the declarations establish the presence of a long-felt need stemming from shortcomings of traditional therapies, which is addressed with surprising clinical benefits and enviable commercial success by the claimed pharmaceutical formulation. These secondary considerations, in total, require a finding that the pending claims are not obvious, and therefore patentable, in view of the prior art of record.

1. The present invention addresses a long-felt need in the art

As set forth in *Graham*, the satisfaction of a long-felt need in the art is evidence of nonobviousness. As explained in detail in the *Rajan Declaration*, the claimed composition represents the fulfillment of a long-felt, but previously unmet, need by patients and healthcare practitioners for management of symptoms of allergic rhinitis (AR) and non-allergic vasomotor rhinitis. The *Rajan Declaration* describes in detail in paragraphs 10, 11, and 12 the long standing problems associated with traditional therapies such as nasal steroids alone, oral antihistamines alone, or combinations of nasal steroids and oral antihistamines. Furthermore, the *Rajan Declaration* explains in paragraphs 13 and 14 how the claimed composition solves many of these long standing problems via its superior efficacy, improved compliance and adherence with treatment, faster response time, and reduced side effects. Accordingly, the *Rajan Declartion* supports a conclusion that the claimed composition represents the fulfillment of a long-felt, but previously unmet, need by patients and healthcare practitioners for management of symptoms of AR and non-allergic vasomotor rhinitis. Accordingly, the invention embodied in the pending claims is not obvious given that it meets the long-felt need outlined above.

2. The present invention solves the long-felt need with surprising clinical 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). The same is equally true in the pharmaceutical arts, which the Federal Circuit has noted are similarly unpredicatable. *See Pfizer Inc. v. Apotex Inc.*, 488 F3d 1377, 82 USPQ2d 1852, 1857 (Fed.Cir. 2007) (Rader, J., dissenting from the denial of rehearing en banc) (referencing the "unpredictable pharmaceutical inventions . . ."). As explained in detail in the *Maus Declaration*, at

the time of the filing of the instant '016 application, the clinically significant effect obtained from administering fluticasone propionate and azelastine hydrochloride in an intranasal pharmaceutical composition would not have been predictable. The *Maus Declaration* describes in paragraphs 7-16 the protocol and results of two clinical studies of the claimed composition. The study results showed that the presently claimed intranasal combination therapy provided five unexpected benefits: (1) an improvement in nasal symptoms as measured by rTNSS, (2) an increase in the number of patients who responded to treatment, (3) a faster response time, (4) improved quality of life, and (5) an improvement in ocular symptoms. These beneficial and superior results associated with the presently claimed intranasal combination therapy were especially surprising in view of extensive studies involving combining a nasal steroid with an oral antihistamine where either no or minimal additional clinical benefit was obtained. The *Maus Declaration* explains in detail in paragraphs 18-22 the disappointing results obtained from studies involving combining a nasal steroid with an oral antihistamine. Moreover, the disappointing results from studies dating back to 1989 further demonstrate the failure of others and the long-felt need described above, and how the unexpected benefits of the claimed composition meet the long-felt need. Accordingly, the *Maus Declartion* supports a conclusion that the superior results obtained for the fluticasone propionate and azelastine hydrochloride combination intranasal formulation, namely, (1) reduced rTNSS, (2) an increase in the number of patients who responded to treatment, (3) a faster response time, (4) improved quality of life, and (5) an improvement in ocular symptoms, would clearly have been unexpected at the time of filing the instant '016 application. Accordingly, the invention embodied in the pending claims is not obvious given that it demonstrates unexpected, beneficial results.

3. The present invention has been commercially successful, leading to copying by others

Commercial success is a strong factor favoring nonobviousness. *See e.g., Akzo N.V. v. United States Int'l Trade Comm'n*, 1 USPQ2d 1241, 1246 (Fed. Cir. 1986). As explained in detail in the *Chopra Declaration*, the sales of Duonase® nasal spray (a commercial embodiment of the claimed composition sold in India), relative to the sales of other subsequent and closely copied brand products in India, indicate a level of commercial success for Duonase® nasal spray that supports the non-obviousness of the claimed composition. The *Chopra Declaration* describes in paragraphs 6 and 8 that Cipla created the market for the claimed composition by launching Duonase® nasal spray in 2004 in India, which sold 167,826 units within the first year thereafter. Paragraphs 9-11 of the *Chopra Declaration* establish that the claimed composition has been widely copied by other companies in India. "Copying is additional evidence of nonobviousness." *Avia Group International Inc. v. L.A. Gear California Inc.*, 853 F2d 1557, 7 USPQ2d 1548, 1554 (Fed.Cir. 1988). The *Chopra Declaration* shows in paragraphs 12 and 13 that the overall market for the claimed formulation has grown at about 21% annually since inception, and that Duonase® nasal spray has maintained a leading role since inception despite the flood of copycat formulations entering the market. Accordingly, the *Chopra Declaration* establishes the commercial success for Duonase® nasal spray as demonstrated by the growth of the overall market since creation by Cipla, the continued growth of sales for Duonase® nasal spray, and the rapid, wide-spread, and on-going copying by competitors supports the non-obviousness of the claimed composition. Accordingly, the invention embodied in the pending claims is not obvious given that it is commercially successful.

4. The secondary considerations require a finding of nonobviousness

As established above, the claimed pharmaceutical formulation fills a long-felt need in the art while displaying unexpected, beneficial results and is commercially successful and copied by others. 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 February 16, 2011 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: 8-16-11

Rodney B. Carroll
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FMC BioPolymer
THE SCIENCE OF FORMULATION

FMC

PRODUCT SPECIFICATION BULLETIN

Avicel® RC-591

microcrystalline cellulose and carboxymethylcellulose sodium NF, Ph. Eur.

Compendial Standards	Specifications
Identification	Passes
Viscosity, 1.2% solids, 120 sec, cps	39 - 91
pH	6.0 - 8.0
Loss on drying, %	NMT 6.0 *
Residue on ignition, %	NMT 5.0
Heavy metals, %	NMT 0.001
Assay for sodium carboxymethycellulose, %	8.3 - 13.8
Clarity of solution	Soluble

Additional FMC Specifications	
Particle size (Air Jet):	
wt. % + 60 mesh (250 microns)	NMT 0.1
wt. % + 325 mesh (45 microns)	NMT 45
Microbial limits:	
Total aerobic microbial count, cfu/g	NMT 100
Total yeast and mold count, cfu/g	NMT 20
Pseudomonas aeruginosa	Absent in a 10g sample
Escherichia coli	Absent in a 10g sample
Staphylococcus aureus	Absent in a 10g sample
Salmonella species	Absent in a 10g sample

This product meets the requirements for Residual Solvents in the *United States Pharmacopeia* <467> and complies with the ICH Guide Q3C for Residual Solvents.

Storage conditions: Store at ambient conditions. Keep containers sealed; material is very hygroscopic.

Re-evaluation date: Three (3) years from date of manufacture, if storage conditions stated above are observed.

Re-evaluation requirements: FMC recommends that after the above re-evaluation date, the customer perform the loss on drying and viscosity tests.

*More restrictive than compendium
NMT = Not More Than

FMC Corporation

FMC BioPolymer

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Because of the numerous factors affecting results, FMC ingredients are sold on the understanding that purchasers will make their own tests to determine the suitability of these products for their particular purpose. The several uses suggested by FMC BioPolymer are presented only to assist our customers in exploring possible applications. All information and data presented are believed to be accurate and reliable, but are presented without the assumption of any liability by FMC BioPolymer.

Technical Service
The information contained in this bulletin is intended to be general in nature. Techniques and data pertaining to specific uses for FMC ingredients and new developments will be published periodically in the form of supplemental application bulletins. Our technical staff is ready to offer assistance in the use of Avicel® microcrystalline cellulose products.

Regulatory Status
Avicel® RC/CL colloid-forming, attrited mixtures of microcrystalline cellulose and carboxymethylcellulose sodium meet the standards set forth in the *United States Pharmacopeia/National Formulary* for microcrystalline cellulose and carboxymethylcellulose sodium and in the *European Pharmacopoeia* for microcrystalline cellulose and carmellose sodium.

Microcrystalline cellulose is generally recognized as safe (GRAS) by qualified experts. FMC maintains a Type IV Drug Master File at the U.S. Food and Drug Administration.

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FMC BioPolymer
THE SCIENCE OF FORMULATION

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PRODUCT SPECIFICATION BULLETIN

Avicel® CL-611

microcrystalline cellulose and carboxymethylcellulose sodium, NF, Ph. Eur.

Compendial Standards	Specifications
Identification	Passes
Viscosity, 2.6% solids, 120 sec, cps	50 - 118
pH	6.0 - 8.0
Loss on drying, %	NMT 6.0 *
Residue on ignition, %	NMT 5.0
Heavy metals, %	NMT 0.001
Assay for sodium carboxymethycellulose, %	11.3 - 18.8
Clarity of solution	Soluble

Additional FMC Specifications	
Particle size (Air Jet):	
wt. % + 60 mesh (250 microns)	NMT 0.1
wt. % + 325 mesh (65 microns)	NMT 50
Microbial limits:	
Total aerobic microbial count, cfu/g	NMT 100
Total yeast and mold count, cfu/g	NMT 20
Pseudomonas aeruginosa	Absent in a 10g sample
Escherichia coli	Absent in a 10g sample
Staphylococcus aureus	Absent in a 10g sample
Salmonella species	Absent in a 10g sample

This product meets the requirements for Residual Solvents in the *United States Pharmacopeia* <467> and complies with the ICH Guide Q3C for Residual Solvents.

Storage conditions: Store at ambient conditions. Keep containers sealed; material is very hygroscopic.

Re-evaluation date: Three (3) years from date of manufacture, if storage conditions stated above are observed.

Re-evaluation requirements: FMC recommends that after the above re-evaluation date, the customer perform the loss on drying and viscosity tests.

*More restrictive than compendium
NMT = Not More Than

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Warranty
Because of the numerous factors affecting results, FMC ingredients are sold on the understanding that purchasers will make their own tests to determine the suitability of these products for their particular purpose. The several uses suggested by FMC BioPolymer are presented only to assist our customers in exploring possible applications. All information and data presented are believed to be accurate and reliable, but are presented without the assumption of any liability by FMC BioPolymer.

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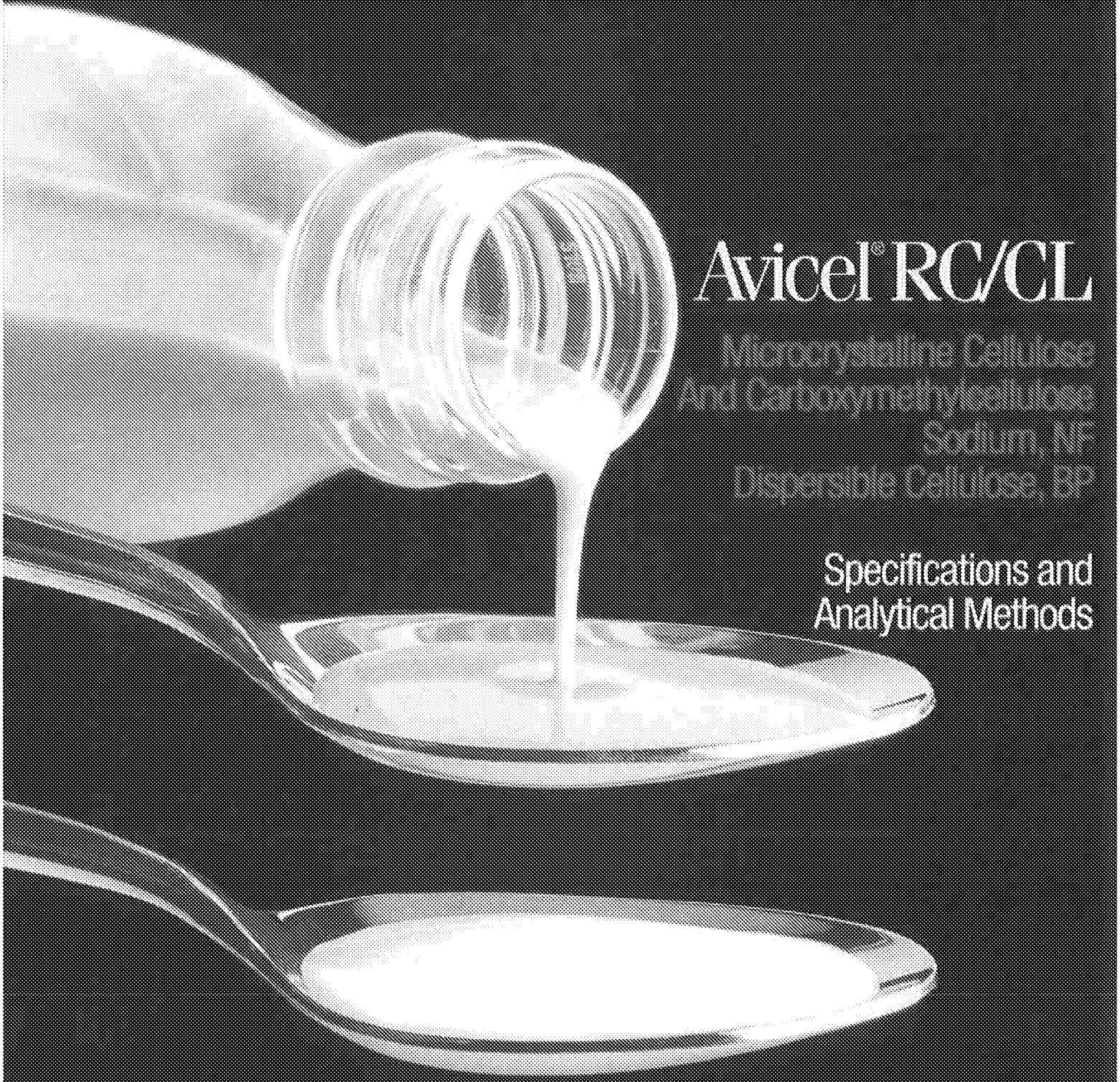


Avicel® RC/CL

Microcrystalline Cellulose And Carboxymethylcellulose Sodium Dispersible Cellulose Gel

Specifications and Analytical Methods

Avicel® RC/CL

Microcrystalline Cellulose and Carboxymethylcellulose Sodium, NF

Introduction

Avicel® RC/CL types of microcrystalline cellulose (MCC) are water dispersible products for use in pharmaceutical preparations. They contain sodium carboxymethylcellulose (NaCMC) to aid dispersion and to serve as a protective colloid.

There are three types of Avicel RC/CL: RC-581, RC-591, and CL-611. All types are off-white, odorless, and tasteless hygroscopic powders. They are insoluble in organic solvents and dilute acids, and partially soluble in both dilute alkali and water (CMC fraction).

To achieve maximum dispersion, RC-581 requires high shear mixing while RC-591 and CL-611 require low shear mixing. With RC-581, RC-591, and CL-611, approximately 60% of the particles in the dispersion are less than 0.2 micron when properly dispersed. Concentrations of less than 1% solids produce fluid dispersions, while concentrations of more than 1.2% solids produce thixotropic gels. CL-611 needs a level slightly higher than 1.2% for thixotropy. Avicel RC-581, RC-591, and CL-611 are listed as microcrystalline cellulose and carboxymethylcellulose sodium in the *U.S. Pharmacopeia/National Formulary* and as dispersible cellulose in the *British Pharmacopoeia*.

Table I — Chemical and Physical Specifications

Microcrystalline Cellulose and Carboxymethylcellulose Sodium, NF			
Product	Avicel RC-581	Avicel RC-591	Avicel CL-611
Loss on drying, %	NMT 5.0	NMT 5.0	NMT 5.0
Ash, %	NMT 3.0	NMT 3.0	NMT 3.0
Sodium carboxymethylcellulose, %	11.0 (min) NMT 15.0	11.0 (min) NMT 15.0	11.0 (min) NMT 15.0
Sodium chloride, %	2.0 (max) NMT 4.0	2.0 (max) NMT 4.0	2.0 (max) NMT 4.0
pH	6.0 - 8.0	6.0 - 8.0	6.0 - 8.0
Viscosity, cps	72 - 108 (1.2% solids)	70 - 91 (1.2% solids)	50 - 110 (2.8% solids)
Residue on sieve, %	NMT 5.0	NMT 5.0	NMT 5.0
Mesh Size			

Table II — Microbiological Specifications

Total aerobic microbial count (cfu/g)	
Total yeast and mold count (cfu/g)	
Escherichia coli	
Salmonella species	
Pseudomonas aeruginosa	
Staphylococcus aureus	

Assay, Sodium Carboxymethylcellulose Content

Follow the procedure outlined in the *USP/NF*.

The assay procedure is based on the fact that Avicel® RC/CL types are produced by drying a blend of microcrystalline cellulose (which contains only trace levels of sodium) with sodium carboxymethylcellulose. The sodium content of sodium carboxymethylcellulose may vary from 6.98 to 8.50% (average 7.75%).

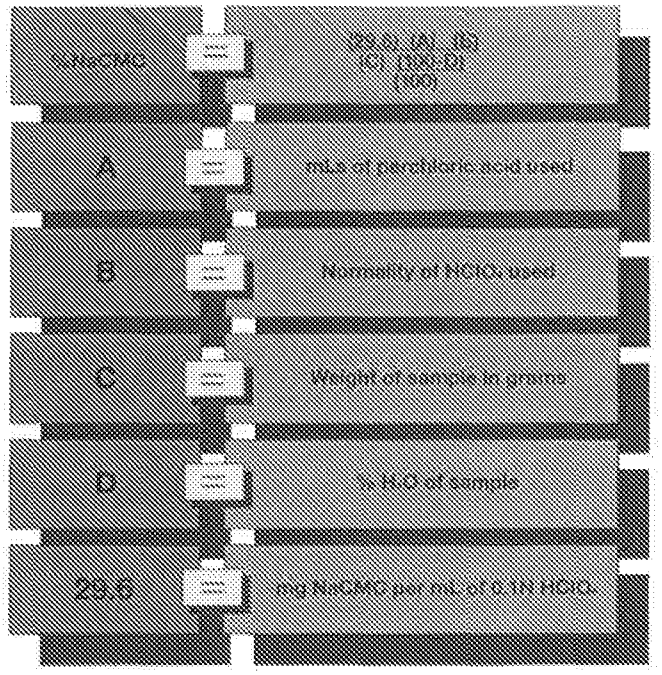
A sodium content of 7.75% corresponds to a degree of substitution of 0.75. For convenience in calculating the results of the assay, the average figure of 7.75% is assumed and used for the sodium content of the sodium carboxymethylcellulose. The percent sodium carboxymethylcellulose in Avicel® RC/CL may be calculated by dividing the percent sodium in an Avicel RC/CL sample by the average percent sodium in sodium carboxymethylcellulose (NaCMC).

Although the quantity of sodium carboxymethylcellulose used in producing Avicel RC /CL is controlled within the limits ± 1%, the assay calculation using Equation 1 may show results of ±2%. This is because the average sodium content of 7.75% is used in Equation 1. If it were practical to determine the exact amount of sodium in each batch of sodium carboxymethylcellulose and to use this figure in the assay calculation instead of the average figure of 7.75%, the assay calculation would, of course, show the true results within the specified manufacturing limits of ±1%. The procedure for measuring the sodium content of sodium carboxymethylcellulose is based on ASTM Designation D1439-83A (Method B, nonaqueous titration).

Procedure

Accurately weigh 2,000 mg of Avicel RC or CL MCC (dry basis) to the nearest mg and transfer to a 250 mL glass-stoppered conical flask. Add 75 mL glacial acetic acid, connect the flask to water-cooled condenser, and reflux gently on a hot plate for 2 hours. Cool to room temperature, transfer the dispersion to a 250 mL beaker with the aid of 50 mL of glacial acetic acid, and titrate 0.1N perchloric acid in dioxane. Determine the endpoint potentiometrically. Each mL of 0.1N perchloric acid is equivalent to 29.6 mg of sodium carboxymethylcellulose.

Table III — Calculations



Viscosity

Follow the procedure outlined in the *USP/NF* <911>.

Absolute viscosity readings in centipoises cannot be measured on Avicel® RC or CL dispersions. Because Avicel RC/CL is a dispersion of microcrystalline cellulose colloidal particles, only an apparent viscosity can be measured. Therefore, the following method must be performed exactly as stated in order to obtain comparable results. Because apparent viscosity is measured, spindle/speed conversions cannot be made.

The test procedure for Avicel RC/CL is based on viscosity readings taken with a Brookfield® viscometer using the No. 1 spindle at 20 rpm. A dispersion* is prepared with a Waring Blendor® mixer, using a 1,000 mL bowl, at a speed of greater than 18,000 rpm with no load. The Waring Blendor speed is controlled by a Powerstat® transformer. A Powerstat setting that provides a line voltage of 115 volts should be used. The Powerstat permits increasing the Waring Blendor speed gradually to avoid splashing.

Procedure

1. Determine the moisture content of Avicel RC/CL powder by drying to a constant weight at 105°C.
2. Add 587±1 mL of distilled or deionized water to the Waring Blendor bowl.
3. Determine the amount of powder, in grams, to be used in preparing the dispersion as follows:
   a) RC-581 and RC-591 use 1.2% dispersion; weight of powder = (594 x 1.2)/% solids of powder.
   b) CL-611 uses 2.6% dispersion; weight of powder = (603 x 2.6)/% solids of powder.
4. Weigh the specified amount of powder to ± 0.01g on weighing paper.
5. Start the Waring Blendor at a Powerstat setting of 30 volts and add the powder to the distilled water. The powder should be added carefully to prevent it from sticking to the sides of the bowl or dropping directly onto the mixing blades. Cover the blender.
6. After the powder has been added and 15 seconds have elapsed since first introducing the powder at a Powerstat setting of 30, adjust the Powerstat setting to 115 volts and mix for two minutes.
7. When the mixing is completed, place the blender bowl under the Brookfield viscometer and lower the No. 1 spindle into the dispersion to the mark on the spindle. Check that viscometer is level and tap the bowl for air bubbles.
8. After 30 seconds have elapsed since the cessation of mixing, start the viscometer spindle rotating at 20 rpm.
9. After the viscometer rotates for 30 seconds, depress clutch, stop the viscometer, and read the value on the 0-100 scale. This value is converted to centipoise by multiplying the reading by a factor of 5.

*A Waring Blendor 700 series (800 series for Europe) should be used for this test.

pH

Follow the procedure outlined in the *USP/NF* <791>; between 6.0 and 8.0 determined on the dispersion prepared in the test for viscosity.

Residue on Ignition

Follow the procedure outlined in the *USP/NF* <281>; not more than 5.0%.

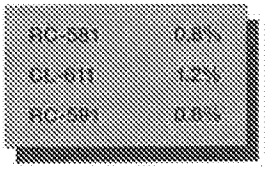
Storage/Stability

Store in cool, dry place and avoid exposure to excessive heat.

This product is hygroscopic and should not be exposed to moisture. It should maintain functional properties for at least two years. Product release specifications are guaranteed at the time of purchase.

Sodium Content

The sodium contribution from the carboxymethylcellulose is typically as follows:



Lot Numbering System

Lot numbers of products are assigned so that product type and time of manufacture may be identified. The characters of a lot number represent as follows:

First character: The product type

Second character: The year of production

Third & fourth characters: The week of production

Fifth character: Site of manufacture

The following provides the information necessary to distinguish between RC /CL types and the manufacturing sites of Avicel microcrystalline cellulose and carboxymethylcellulose sodium, NF.

First Character	Fifth Character
B = RC-581	N = Newark, DE manufacturing site
D = RC-591	C = Cork, Ireland manufacturing site
E = CL-611	

Rheological Properties

Avicel® RC/CL gels are highly thixotropic and have a finite yield value at low concentrations. Please refer to the Avicel® RC-591 applications brochure for additional information on rheological properties and applications.

Preparation of Colloidal Dispersions

Analytical results, as well as applications of Avicel RC/CL types, depend on the development of maximum colloidal dispersions. Dispersions should be prepared with USP purified water. Recommended mixers include: Cowles® dissolver, Waring Blendor® mixer, and colloid mill for RC-581; and Lightnin'® mixer for RC-591 and CL-611. Additional dispersion information is included in the RC-591 applications brochure.

Analytical Procedures for Avicel RC/CL

Description

Avicel RC/CL types are colloidal forms of microcrystalline cellulose which have been blended with sodium carboxymethylcellulose and coprocessed. They are white, odorless, hygroscopic powders. They are readily dispersed in water with moderate to high shear mixing to form white, opaque, colloidal thixotropic gels. Avicel RC/CL types are insoluble in organic solvents and dilute acids, and partially soluble in both dilute alkali and water (CMC fraction).

Identification

Follow the procedure in the *U.S. Pharmacopeial/National Formulary*.

1. Add 6 grams of powder to 300 mL of distilled water contained in a 1,000 mL Waring Blendor® bowl and stir at line voltage of 115 volts (18,000 rpm) for 5 minutes: a white, opaque, bubble-free dispersion forms that does not sediment on standing.
2. Add several drops of the dispersion prepared above to a 10% aluminum chloride solution; each drop coagulates into a white, opaque clot that does not disperse on standing.
3. The dispersion is not colored purplish blue to blue by iodine test solution.

Loss on Drying

Follow the procedure outlined in the *USP/NF* <731>.

Dry Avicel RC/CL to a constant weight at 105°C.

Heavy Metals

Follow the procedure outlined in the *USP/NF* using Method II <231>; 0.001%.

Table IV — Particle Size

Measure the percent retained on the corresponding screen below using an Alpine® air jet sieve, model 200, at a vacuum of approximately 10–12 inches of water using the amount of powder and time as specified below.

Type	Mesh Size	Percent	Time (minutes)
RC-581	+ 60	10	3
RC-581	+325	50	3
RC-591	+ 60	10	3
RC-591	+325	50	3
CL-611	+ 60	10	3
CL-611	+325	50	3

Note: Different methods of sieving particle size determination such as Ro-Tap® stack sieve, laser diffraction, and sonic sifter will yield different results.

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Patents

FMC Corporation does not warrant against infringement of patents of third parties by reason of any uses made of the product in combination with other material or in the operation of any process, and purchasers assume all risks of patent infringement by reason of any such use, combination or operation.

The products, processes and uses thereof described herein are covered by one or more patent applications or patents.

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Avicel RC/CL, a colloid forming attrited mixture of microcrystalline cellulose and carboxymethylcellulose sodium, meet the standards set forth in the *United States Pharmacopoeia/National Formulary* for "microcrystalline cellulose and carboxymethylcellulose sodium" and in the *British Pharmacopoeia* for dispersible cellulose.

The colloid forming attrited mixtures of microcrystalline cellulose and sodium carboxymethylcellulose are generally recognized as safe (GRAS) by qualified experts. FMC maintains a Type IV Drug Master File (Excipients) to support the use of Avicel RC/CL in drug products.

RC-16 Updated 10/96
(2/99)

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

STABILITY TESTING OF NEW DRUG SUBSTANCES AND PRODUCTS Q1A(R2)

Recommended for Adoption
at Step 4 of the ICH Process
on 6 February 2003
by the ICH Steering Committee

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

COVER NOTE FOR REVISION OF Q1A(R)
STABILITY TESTING OF
NEW DRUG SUBSTANCES AND PRODUCTS

The purpose of this note is to outline the changes made in Q1A(R) that result from adoption of ICH Q1F "Stability Data Package for Registration Applications in Climatic Zones III and IV". These changes are:

1. The intermediate storage condition has been changed from 30°C ± 2°C/60% RH ± 5% RH to 30°C ± 2°C/65% RH ± 5% RH in the following sections:
   - 2.1.7.1 Drug Substance - Storage Conditions - General Case
   - 2.2.7.1 Drug Product - Storage Conditions - General Case
   - 2.2.7.3 Drug products packaged in semi-permeable containers
   - 3 Glossary - "Intermediate testing"

2. 30°C ± 2°C/65% RH ± 5% RH can be a suitable alternative long-term storage condition to 25°C ± 2°C/60% RH ± 5% in the following sections:
   - 2.1.7.1 Drug Substance - Storage Conditions - General Case
   - 2.2.7.1 Drug Product - Storage Conditions - General Case

3. 30°C ± 2°C/35% RH ± 5% RH has been added as a suitable alternative long-term storage condition to 25°C ± 2°C/40% RH ± 5% and the corresponding example for the ratio of water-loss rates has been included in the following section:
   - 2.2.7.3 Drug products packaged in semi-permeable containers

Mid-stream switch of the intermediate storage condition from 30°C ± 2°C/60% RH ± 5% RH to 30°C ± 2°C/65% RH ± 5% RH can be appropriate provided that the respective storage conditions and the date of the switch are clearly documented and stated in the registration application.

It is recommended that registration applications contain data from complete studies at the intermediate storage condition 30°C ± 2°C/65% RH ± 5% RH, if applicable, by three years after the date of publication of this revised guideline in the respective ICH tripartite region.

STABILITY TESTING OF
STABILITY TESTING OF NEW DRUG SUBSTANCES AND PRODUCTS

ICH Harmonised Tripartite Guideline

First Recommended for Adoption at *Step 4* of the ICH Process on 27 October 1993.

Revised under *Step 2* of the ICH Process on 7 October 1999 and Recommended for Adoption at *Step 4* of the ICH Process on 8 November 2000.

This guideline has been Revised a second time and has reached *Step 4* of the ICH Process at the ICH Steering Committee meeting on 6 February 2003. It is recommended for adoption to the three regulatory parties to ICH

TABLE OF CONTENTS

STABILITY TESTING OF NEW DRUG SUBSTANCES AND PRODUCTS

1. INTRODUCTION

1.1. Objectives of the Guideline

The following guideline is a revised version of the ICH Q1A guideline and defines the stability data package for a new drug substance or drug product that is sufficient for a registration application within the three regions of the EC, Japan, and the United States. It does not seek necessarily to cover the testing for registration in or export to other areas of the world.

The guideline seeks to exemplify the core stability data package for new drug substances and products, but leaves sufficient flexibility to encompass the variety of different practical situations that may be encountered due to specific scientific considerations and characteristics of the materials being evaluated. Alternative approaches can be used when there are scientifically justifiable reasons.

1.2. Scope of the Guideline

The guideline addresses the information to be submitted in registration applications for new molecular entities and associated drug products. This guideline does not currently seek to cover the information to be submitted for abbreviated or abridged applications, variations, clinical trial applications, etc.

Specific details of the sampling and testing for particular dosage forms in their proposed container closures are not covered in this guideline.

Further guidance on new dosage forms and on biotechnological/biological products can be found in ICH guidelines Q1C and Q5C, respectively.

1.3. General Principles

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, and to establish a re-test period for the drug substance or a shelf life for the drug product and recommended storage conditions.

The choice of test conditions defined in this guideline is based on an analysis of the effects of climatic conditions in the three regions of the EC, Japan and the United States. The mean kinetic temperature in any part of the world can be derived from climatic data, and the world can be divided into four climatic zones, I-IV. This guideline addresses climatic zones I and II. The principle has been established that stability information generated in any one of the three regions of the EC, Japan and the United States would be mutually acceptable to the other two regions, provided the information is consistent with this guideline and the labeling is in accord with national/regional requirements.

2. GUIDELINES

2.1. Drug Substance

2.1.1. General

Information on the stability of the drug substance is an integral part of the systematic approach to stability evaluation.

2.1.2. Stress Testing

Stress testing of the drug substance can help identify the likely degradation products, which can in turn help establish the degradation pathways and the intrinsic stability of the molecule and validate the stability indicating power of the analytical procedures used. The nature of the stress testing will depend on the individual drug substance and the type of drug product involved.

Stress testing is likely to be carried out on a single batch of the drug substance. It should include the effect of temperatures (in 10°C increments (e.g., 50°C, 60°C, etc.) above that for accelerated testing), humidity (e.g., 75% RH or greater) where appropriate, oxidation, and photolysis on the drug substance. The testing should also evaluate the susceptibility of the drug substance to hydrolysis across a wide range of pH values when in solution or suspension. Photostability testing should be an integral part of stress testing. The standard conditions for photostability testing are described in ICH Q1B.

Examining degradation products under stress conditions is useful in establishing degradation pathways and developing and validating suitable analytical procedures. However, it may not be necessary to examine specifically for certain degradation products if it has been demonstrated that they are not formed under accelerated or long term storage conditions.

Results from these studies will form an integral part of the information provided to regulatory authorities.

2.1.3. Selection of Batches

Data from formal stability studies should be provided on at least three primary batches of the drug substance. The batches should be manufactured to a minimum of pilot scale by the same synthetic route as, and using a method of manufacture and procedure that simulates the final process to be used for, production batches. The overall quality of the batches of drug substance placed on formal stability studies should be representative of the quality of the material to be made on a production scale.

Other supporting data can be provided.

2.1.4. Container Closure System

The stability studies should be conducted on the drug substance packaged in a container closure system that is the same as or simulates the packaging proposed for storage and distribution.

2.1.5. Specification

Specification, which is a list of tests, reference to analytical procedures, and proposed acceptance criteria, is addressed in ICH Q6A and Q6B. In addition, specification for degradation products in a drug substance is discussed in Q3A.

Stability studies should include testing of those attributes of the drug substance that are susceptible to change during storage and are likely to influence quality, safety, and/or efficacy. The testing should cover, as appropriate, the physical, chemical, biological, and microbiological attributes. Validated stability-indicating analytical procedures should be applied. Whether and to what extent replication should be performed will depend on the results from validation studies.

2.1.6. Testing Frequency

For long term studies, frequency of testing should be sufficient to establish the stability profile of the drug substance. For drug substances with a proposed re-test period of at least 12 months, the frequency of testing at the long term storage condition should normally be every 3 months over the first year, every 6 months over the second year, and annually thereafter through the proposed re-test period.

At the accelerated storage condition, a minimum of three time points, including the initial and final time points (e.g., 0, 3, and 6 months), from a 6-month study is recommended. Where an expectation (based on development experience) exists that results from accelerated studies are likely to approach significant change criteria, increased testing should be conducted either by adding samples at the final time point or by including a fourth time point in the study design.

When testing at the intermediate storage condition is called for as a result of significant change at the accelerated storage condition, a minimum of four time points, including the initial and final time points (e.g., 0, 6, 9, 12 months), from a 12-month study is recommended.

2.1.7. Storage Conditions

In general, a drug substance should be evaluated under storage conditions (with appropriate tolerances) that test its thermal stability and, if applicable, its sensitivity to moisture. The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment, and subsequent use.

The long term testing should cover a minimum of 12 months' duration on at least three primary batches at the time of submission and should be continued for a period of time sufficient to cover the proposed re-test period. Additional data accumulated during the assessment period of the registration application should be submitted to the authorities if requested. Data from the accelerated storage condition and, if appropriate, from the intermediate storage condition can be used to evaluate the effect of short term excursions outside the label storage conditions (such as might occur during shipping).

Long term, accelerated, and, where appropriate, intermediate storage conditions for drug substances are detailed in the sections below. The general case applies if the drug substance is not specifically covered by a subsequent section. Alternative storage conditions can be used if justified.

2.1.7.1. General case

Study	Storage condition	Minimum time period covered by data at submission
Long term*	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH	12 months
Intermediate**	30°C ± 2°C/65% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months

*It is up to the applicant to decide whether long term stability studies are performed at 25 ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH.

**If 30°C ± 2°C/65% RH ± 5% RH is the long-term condition, there is no intermediate condition.

If long-term studies are conducted at 25°C ± 2°C/60% RH ± 5% RH and "significant change" occurs at any time during 6 months' testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria. Testing at the intermediate storage condition should include all tests, unless otherwise justified. The initial application should include a minimum of 6 months' data from a 12-month study at the intermediate storage condition.

"Significant change" for a drug substance is defined as failure to meet its specification.

2.1.7.2. Drug substances intended for storage in a refrigerator

Study	Storage condition	Minimum time period covered by data at submission
Long term	5°C ± 3°C	12 months
Accelerated	25°C ± 2°C/60% RH ± 5% RH	6 months

Data from refrigerated storage should be assessed according to the evaluation section of this guideline, except where explicitly noted below.

If significant change occurs between 3 and 6 months' testing at the accelerated storage condition, the proposed re-test period should be based on the real time data available at the long term storage condition.

If significant change occurs within the first 3 months' testing at the accelerated storage condition, a discussion should be provided to address the effect of short term excursions outside the label storage condition, e.g., during shipping or handling. This discussion can be supported, if appropriate, by further testing on a single batch of the drug substance for a period shorter than 3 months but with more frequent testing than usual. It is considered unnecessary to continue to test a drug substance through 6 months when a significant change has occurred within the first 3 months.

2.1.7.3. Drug substances intended for storage in a freezer

Study	Storage condition	Minimum time period covered by data at submission
Long term	- 20°C ± 5°C	12 months

For drug substances intended for storage in a freezer, the re-test period should be based on the real time data obtained at the long term storage condition. In the absence of an accelerated storage condition for drug substances intended to be stored in a freezer, testing on a single batch at an elevated temperature (e.g., 5°C ± 3°C or 25°C ± 2°C) for an appropriate time period should be conducted to address the effect of short term excursions outside the proposed label storage condition, e.g., during shipping or handling.

2.1.7.4. Drug substances intended for storage below -20°C

Drug substances intended for storage below -20°C should be treated on a case-by-case basis.

2.1.8. Stability Commitment

When available long term stability data on primary batches do not cover the proposed re-test period granted at the time of approval, a commitment should be made to continue the stability studies post approval in order to firmly establish the re-test period.

Where the submission includes long term stability data on three production batches covering the proposed re-test period, a post approval commitment is considered unnecessary. Otherwise, one of the following commitments should be made:

1. If the submission includes data from stability studies on at least three production batches, a commitment should be made to continue these studies through the proposed re-test period.
2. If the submission includes data from stability studies on fewer than three production batches, a commitment should be made to continue these studies through the proposed re-test period and to place additional production batches, to a total of at least three, on long term stability studies through the proposed re-test period.
3. If the submission does not include stability data on production batches, a commitment should be made to place the first three production batches on long term stability studies through the proposed re-test period.

The stability protocol used for long term studies for the stability commitment should be the same as that for the primary batches, unless otherwise scientifically justified.

2.1.9. Evaluation

The purpose of the stability study is to establish, based on testing a minimum of three batches of the drug substance and evaluating the stability information (including, as appropriate, results of the physical, chemical, biological, and microbiological tests), a re-test period applicable to all future batches of the drug substance manufactured under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification throughout the assigned re-test period.

The data may show so little degradation and so little variability that it is apparent from looking at the data that the requested re-test period will be granted. Under these circumstances, it is normally unnecessary to go through the formal statistical analysis; providing a justification for the omission should be sufficient.

An approach for analyzing the data on a quantitative attribute that is expected to change with time is to determine the time at which the 95% one-sided confidence limit for the mean curve intersects the acceptance criterion. If analysis shows that the batch-to-batch variability is small, it is advantageous to combine the data into one overall estimate. This can be done by first applying appropriate statistical tests (e.g., p values for level of significance of rejection of more than 0.25) to the slopes of the regression lines and zero time intercepts for the individual batches. If it is inappropriate to combine data from several batches, the overall re-test period should be based on the minimum time a batch can be expected to remain within acceptance criteria.

The nature of any degradation relationship will determine whether the data should be transformed for linear regression analysis. Usually the relationship can be represented by a linear, quadratic, or cubic function on an arithmetic or logarithmic scale. Statistical methods should be employed to test the goodness of fit of the data on all batches and combined batches (where appropriate) to the assumed degradation line or curve.

Limited extrapolation of the real time data from the long term storage condition beyond the observed range to extend the re-test period can be undertaken at approval time, if justified. This justification should be based on what is known about the mechanism of degradation, the results of testing under accelerated conditions, the goodness of fit of any mathematical model, batch size, existence of supporting stability data, etc. However, this extrapolation assumes that the same degradation relationship will continue to apply beyond the observed data.

Any evaluation should cover not only the assay, but also the levels of degradation products and other appropriate attributes.

2.1.10. Statements/Labeling

A storage statement should be established for the labeling in accordance with relevant national/regional requirements. The statement should be based on the stability evaluation of the drug substance. Where applicable, specific instructions should be provided, particularly for drug substances that cannot tolerate freezing. Terms such as "ambient conditions" or "room temperature" should be avoided.

A re-test period should be derived from the stability information, and a retest date should be displayed on the container label if appropriate.

2.2. Drug Product

2.2.1. General

The design of the formal stability studies for the drug product should be based on knowledge of the behavior and properties of the drug substance and from stability studies on the drug substance and on experience gained from clinical formulation studies. The likely changes on storage and the rationale for the selection of attributes to be tested in the formal stability studies should be stated.

2.2.2. Photostability Testing

Photostability testing should be conducted on at least one primary batch of the drug product if appropriate. The standard conditions for photostability testing are described in ICH Q1B.

2.2.3. Selection of Batches

Data from stability studies should be provided on at least three primary batches of the drug product. The primary batches should be of the same formulation and packaged in the same container closure system as proposed for marketing. The manufacturing process used for primary batches should simulate that to be applied to production batches and should provide product of the same quality and meeting the same specification as that intended for marketing. Two of the three batches should be at least pilot scale batches and the third one can be smaller, if justified. Where possible, batches of the drug product should be manufactured by using different batches of the drug substance.

Stability studies should be performed on each individual strength and container size of the drug product unless bracketing or matrixing is applied.

Other supporting data can be provided.

2.2.4. Container Closure System

Stability testing should be conducted on the dosage form packaged in the container closure system proposed for marketing (including, as appropriate, any secondary packaging and container label). Any available studies carried out on the drug product outside its immediate container or in other packaging materials can form a useful part of the stress testing of the dosage form or can be considered as supporting information, respectively.

2.2.5. Specification

Specification, which is a list of tests, reference to analytical procedures, and proposed acceptance criteria, including the concept of different acceptance criteria for release and shelf life specifications, is addressed in ICH Q6A and Q6B. In addition, specification for degradation products in a drug product is addressed in Q3B.

Stability studies should include testing of those attributes of the drug product that are susceptible to change during storage and are likely to influence quality, safety, and/or efficacy. The testing should cover, as appropriate, the physical, chemical, biological, and microbiological attributes, preservative content (e.g., antioxidant, antimicrobial preservative), and functionality tests (e.g., for a dose delivery system). Analytical procedures should be fully validated and stability indicating. Whether and to what extent replication should be performed will depend on the results of validation studies.

Shelf life acceptance criteria should be derived from consideration of all available stability information. It may be appropriate to have justifiable differences between the shelf life and release acceptance criteria based on the stability evaluation and the changes observed on storage. Any differences between the release and shelf life acceptance criteria for antimicrobial preservative content should be supported by a validated correlation of chemical content and preservative effectiveness demonstrated during drug development on the product in its final formulation (except for preservative concentration) intended for marketing. A single primary stability batch of the drug product should be tested for antimicrobial preservative effectiveness (in addition to preservative content) at the proposed shelf life for verification purposes, regardless of whether there is a difference between the release and shelf life acceptance criteria for preservative content.

2.2.6. Testing Frequency

For long term studies, frequency of testing should be sufficient to establish the stability profile of the drug product. For products with a proposed shelf life of at least 12 months, the frequency of testing at the long term storage condition should normally be every 3 months over the first year, every 6 months over the second year, and annually thereafter through the proposed shelf life.

At the accelerated storage condition, a minimum of three time points, including the initial and final time points (e.g., 0, 3, and 6 months), from a 6-month study is recommended. Where an expectation (based on development experience) exists that results from accelerated testing are likely to approach significant change criteria, increased testing should be conducted either by adding samples at the final time point or by including a fourth time point in the study design.

When testing at the intermediate storage condition is called for as a result of significant change at the accelerated storage condition, a minimum of four time points, including the initial and final time points (e.g., 0, 6, 9, 12 months), from a 12-month study is recommended.

Reduced designs, i.e., matrixing or bracketing, where the testing frequency is reduced or certain factor combinations are not tested at all, can be applied, if justified.

2.2.7. Storage Conditions

In general, a drug product should be evaluated under storage conditions (with appropriate tolerances) that test its thermal stability and, if applicable, its sensitivity to moisture or potential for solvent loss. The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment, and subsequent use.

Stability testing of the drug product after constitution or dilution, if applicable, should be conducted to provide information for the labeling on the preparation, storage condition, and in-use period of the constituted or diluted product. This testing should be performed on the constituted or diluted product through the proposed in-use period on primary batches as part of the formal stability studies at initial and final time points and, if full shelf life long term data will not be available before submission, at 12 months or the last time point for which data will be available. In general, this testing need not be repeated on commitment batches.

The long term testing should cover a minimum of 12 months' duration on at least three primary batches at the time of submission and should be continued for a period of time sufficient to cover the proposed shelf life. Additional data accumulated during the assessment period of the registration application should be submitted to the authorities if requested. Data from the accelerated storage condition and, if appropriate, from the intermediate storage condition can be used to evaluate the effect of short term excursions outside the label storage conditions (such as might occur during shipping).

Long term, accelerated, and, where appropriate, intermediate storage conditions for drug products are detailed in the sections below. The general case applies if the drug product is not specifically covered by a subsequent section. Alternative storage conditions can be used, if justified.

2.2.7.1. General case

Study	Storage condition	Minimum time period covered by data at submission
Long term*	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH	12 months
Intermediate**	30°C ± 2°C/65% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months

*It is up to the applicant to decide whether long term stability studies are performed at 25 ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH.

**If 30°C ± 2°C/65% RH ± 5% RH is the long-term condition, there is no intermediate condition.

If long-term studies are conducted at 25°C ± 2°C/60% RH ± 5% RH and "significant change" occurs at any time during 6 months' testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria. The initial application should include a minimum of 6 months' data from a 12-month study at the intermediate storage condition.

In general, "significant change" for a drug product is defined as:

1. A 5% change in assay from its initial value; or failure to meet the acceptance criteria for potency when using biological or immunological procedures;
2. Any degradation product's exceeding its acceptance criterion;
3. Failure to meet the acceptance criteria for appearance, physical attributes, and functionality test (e.g., color, phase separation, resuspendibility, caking, hardness, dose delivery per actuation); however, some changes in physical attributes (e.g., softening of suppositories, melting of creams) may be expected under accelerated conditions;

and, as appropriate for the dosage form:

4. Failure to meet the acceptance criterion for pH; or
5. Failure to meet the acceptance criteria for dissolution for 12 dosage units.

2.2.7.2. Drug products packaged in impermeable containers

Sensitivity to moisture or potential for solvent loss is not a concern for drug products packaged in impermeable containers that provide a permanent barrier to passage of moisture or solvent. Thus, stability studies for products stored in impermeable containers can be conducted under any controlled or ambient humidity condition.

2.2.7.3. Drug products packaged in semi-permeable containers

Aqueous-based products packaged in semi-permeable containers should be evaluated for potential water loss in addition to physical, chemical, biological, and microbiological stability. This evaluation can be carried out under conditions of low relative humidity, as discussed below. Ultimately, it should be demonstrated that aqueous-based drug products stored in semi-permeable containers can withstand low relative humidity environments.

Other comparable approaches can be developed and reported for non-aqueous, solvent-based products.

Study	Storage condition	Minimum time period covered by data at submission
Long term*	25°C ± 2°C/40% RH ± 5% RH or 30°C ± 2°C/35% RH ± 5% RH	12 months
Intermediate**	30°C ± 2°C/65% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C/not more than (NMT) 25% RH	6 months

*It is up to the applicant to decide whether long term stability studies are performed at 25 ± 2°C/40% RH ± 5% RH or 30°C ± 2°C/35% RH ± 5% RH.

**If 30°C ± 2°C/35% RH ± 5% RH is the long-term condition, there is no intermediate condition.

For long-term studies conducted at 25°C ± 2°C/40% RH ± 5% RH, additional testing at the intermediate storage condition should be performed as described under the general case to evaluate the temperature effect at 30°C if significant change other than water loss occurs during the 6 months' testing at the accelerated storage condition. A significant change in water loss alone at the accelerated storage condition does not necessitate testing at the intermediate storage condition. However, data should be provided to demonstrate that the drug product will not have significant water loss throughout the proposed shelf life if stored at 25°C and the reference relative humidity of 40% RH.

A 5% loss in water from its initial value is considered a significant change for a product packaged in a semi-permeable container after an equivalent of 3 months' storage at 40°C/NMT 25% RH. However, for small containers (1 mL or less) or unit-dose products, a water loss of 5% or more after an equivalent of 3 months' storage at 40°C/NMT 25% RH may be appropriate, if justified.

An alternative approach to studying at the reference relative humidity as recommended in the table above (for either long term or accelerated testing) is performing the stability studies under higher relative humidity and deriving the water loss at the reference relative humidity through calculation. This can be achieved by experimentally determining the permeation coefficient for the container closure system or, as shown in the example below, using the calculated ratio of water loss rates between the two humidity conditions at the same temperature. The permeation coefficient for a container closure system can be experimentally determined by using the worst case scenario (e.g., the most diluted of a series of concentrations) for the proposed drug product.

Example of an approach for determining water loss:

For a product in a given container closure system, container size, and fill, an appropriate approach for deriving the water loss rate at the reference relative humidity is to multiply the water loss rate measured at an alternative relative humidity at the same temperature by a water loss rate ratio shown in the table below. A linear water loss rate at the alternative relative humidity over the storage period should be demonstrated.

For example, at a given temperature, e.g., 40°C, the calculated water loss rate during storage at NMT 25% RH is the water loss rate measured at 75% RH multiplied by 3.0, the corresponding water loss rate ratio.

Alternative relative humidity	Reference relative humidity	Ratio of water loss rates at a given temperature
60% RH	25% RH	1.9
60% RH	40% RH	1.5
65% RH	35% RH	1.9
75% RH	25% RH	3.0

Valid water loss rate ratios at relative humidity conditions other than those shown in the table above can also be used.

2.2.7.4. Drug products intended for storage in a refrigerator

Study	Storage condition	Minimum time period covered by data at submission
Long term	5°C ± 3°C	12 months
Accelerated	25°C ± 2°C/60% RH ± 5% RH	6 months

If the drug product is packaged in a semi-permeable container, appropriate information should be provided to assess the extent of water loss.

Data from refrigerated storage should be assessed according to the evaluation section of this guideline, except where explicitly noted below.

If significant change occurs between 3 and 6 months' testing at the accelerated storage condition, the proposed shelf life should be based on the real time data available from the long term storage condition.

If significant change occurs within the first 3 months' testing at the accelerated storage condition, a discussion should be provided to address the effect of short term excursions outside the label storage condition, e.g., during shipment and handling. This discussion can be supported, if appropriate, by further testing on a single batch of the drug product for a period shorter than 3 months but with more frequent testing than usual. It is considered unnecessary to continue to test a product through 6 months when a significant change has occurred within the first 3 months.

2.2.7.5. Drug products intended for storage in a freezer

Study	Storage condition	Minimum time period covered by data at submission
Long term	- 20°C ± 5°C	12 months

For drug products intended for storage in a freezer, the shelf life should be based on the real time data obtained at the long term storage condition. In the absence of an accelerated storage condition for drug products intended to be stored in a freezer, testing on a single batch at an elevated temperature (e.g., 5°C ± 3°C or 25°C ± 2°C) for an appropriate time period should be conducted to address the effect of short term excursions outside the proposed label storage condition.

2.2.7.6. Drug products intended for storage below -20°C

Drug products intended for storage below -20°C should be treated on a case-by-case basis.

2.2.8. Stability Commitment

When available long term stability data on primary batches do not cover the proposed shelf life granted at the time of approval, a commitment should be made to continue the stability studies post approval in order to firmly establish the shelf life.

Where the submission includes long term stability data from three production batches covering the proposed shelf life, a post approval commitment is considered unnecessary. Otherwise, one of the following commitments should be made:

1. If the submission includes data from stability studies on at least three production batches, a commitment should be made to continue the long term studies through the proposed shelf life and the accelerated studies for 6 months.
2. If the submission includes data from stability studies on fewer than three production batches, a commitment should be made to continue the long term studies through the proposed shelf life and the accelerated studies for 6 months, and to place additional production batches, to a total of at least three, on long term stability studies through the proposed shelf life and on accelerated studies for 6 months.
3. If the submission does not include stability data on production batches, a commitment should be made to place the first three production batches on long term stability studies through the proposed shelf life and on accelerated studies for 6 months.

The stability protocol used for studies on commitment batches should be the same as that for the primary batches, unless otherwise scientifically justified.

Where intermediate testing is called for by a significant change at the accelerated storage condition for the primary batches, testing on the commitment batches can be conducted at either the intermediate or the accelerated storage condition. However, if significant change occurs at the accelerated storage condition on the commitment batches, testing at the intermediate storage condition should also be conducted.

2.2.9. Evaluation

A systematic approach should be adopted in the presentation and evaluation of the stability information, which should include, as appropriate, results from the physical, chemical, biological, and microbiological tests, including particular attributes of the dosage form (for example, dissolution rate for solid oral dosage forms).

The purpose of the stability study is to establish, based on testing a minimum of three batches of the drug product, a shelf life and label storage instructions applicable to all future batches of the drug product manufactured and packaged under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification throughout its shelf life.

Where the data show so little degradation and so little variability that it is apparent from looking at the data that the requested shelf life will be granted, it is normally unnecessary to go through the formal statistical analysis; providing a justification for the omission should be sufficient.

An approach for analyzing data of a quantitative attribute that is expected to change with time is to determine the time at which the 95 one-sided confidence limit for the mean curve intersects the acceptance criterion. If analysis shows that the batch-to-batch variability is small, it is advantageous to combine the data into one overall estimate. This can be done by first applying appropriate statistical tests (e.g., p values for level of significance of rejection of more than 0.25) to the slopes of the regression lines and zero time intercepts for the individual batches. If it is inappropriate to combine data from several batches, the overall shelf life should be based on the minimum time a batch can be expected to remain within acceptance criteria.

The nature of the degradation relationship will determine whether the data should be transformed for linear regression analysis. Usually the relationship can be represented by a linear, quadratic, or cubic function on an arithmetic or logarithmic scale. Statistical methods should be employed to test the goodness of fit on all batches and combined batches (where appropriate) to the assumed degradation line or curve.

Limited extrapolation of the real time data from the long term storage condition beyond the observed range to extend the shelf life can be undertaken at approval time, if justified. This justification should be based on what is known about the mechanisms of degradation, the results of testing under accelerated conditions, the goodness of fit of any mathematical model, batch size, existence of supporting stability data, etc. However, this extrapolation assumes that the same degradation relationship will continue to apply beyond the observed data.

Any evaluation should consider not only the assay but also the degradation products and other appropriate attributes. Where appropriate, attention should be paid to reviewing the adequacy of the mass balance and different stability and degradation performance.

2.2.10. Statements/Labeling

A storage statement should be established for the labeling in accordance with relevant national/regional requirements. The statement should be based on the stability evaluation of the drug product. Where applicable, specific instruction should be provided, particularly for drug products that cannot tolerate freezing. Terms such as “ambient conditions” or “room temperature” should be avoided.

There should be a direct link between the label storage statement and the demonstrated stability of the drug product. An expiration date should be displayed on the container label.

3. GLOSSARY

The following definitions are provided to facilitate interpretation of the guideline.

Accelerated testing

Studies designed to increase the rate of chemical degradation or physical change of a drug substance or drug product by using exaggerated storage conditions as part of the formal stability studies. Data from these studies, in addition to long term stability studies, can be used to assess longer term chemical effects at non-accelerated conditions and to evaluate the effect of short term excursions outside the label storage conditions such as might occur during shipping. Results from accelerated testing studies are not always predictive of physical changes.

Bracketing

The design of a stability schedule such that only samples on the extremes of certain design factors, e.g., strength, package size, are tested at all time points as in a full design. The design assumes that the stability of any intermediate levels is represented by the stability of the extremes tested. Where a range of strengths is to be tested, bracketing is applicable if the strengths are identical or very closely related in composition (e.g., for a tablet range made with different compression weights of a similar basic granulation, or a capsule range made by filling different plug fill weights of the same basic composition into different size capsule shells). Bracketing can be applied to different container sizes or different fills in the same container closure system.

Climatic zones

The four zones in the world that are distinguished by their characteristic prevalent annual climatic conditions. This is based on the concept described by W. Grimm (*Drugs Made in Germany*, 28:196-202, 1985 and 29:39-47, 1986).

Commitment batches

Production batches of a drug substance or drug product for which the stability studies are initiated or completed post approval through a commitment made in the registration application.

Container closure system

The sum of packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection to the drug product. A packaging system is equivalent to a container closure system.

Dosage form

A pharmaceutical product type (e.g., tablet, capsule, solution, cream) that contains a drug substance generally, but not necessarily, in association with excipients.

Drug product

The dosage form in the final immediate packaging intended for marketing.

Drug substance

The unformulated drug substance that may subsequently be formulated with excipients to produce the dosage form.

Excipient

Anything other than the drug substance in the dosage form.

Expiration date

The date placed on the container label of a drug product designating the time prior to which a batch of the product is expected to remain within the approved shelf life specification if stored under defined conditions, and after which it must not be used.

Formal stability studies

Long term and accelerated (and intermediate) studies undertaken on primary and/or commitment batches according to a prescribed stability protocol to establish or confirm the re-test period of a drug substance or the shelf life of a drug product.

Impermeable containers

Containers that provide a permanent barrier to the passage of gases or solvents, e.g., sealed aluminum tubes for semi-solids, sealed glass ampoules for solutions.

Intermediate testing

Studies conducted at 30°C/65% RH and designed to moderately increase the rate of chemical degradation or physical changes for a drug substance or drug product intended to be stored long term at 25°C.

Long term testing

Stability studies under the recommended storage condition for the re-test period or shelf life proposed (or approved) for labeling.

Mass balance

The process of adding together the assay value and levels of degradation products to see how closely these add up to 100% of the initial value, with due consideration of the margin of analytical error.

Matrixing

The design of a stability schedule such that a selected subset of the total number of possible samples for all factor combinations is tested at a specified time point. At a subsequent time point, another subset of samples for all factor combinations is tested. The design assumes that the stability of each subset of samples tested represents the stability of all samples at a given time point. The differences in the samples for the same drug product should be identified as, for example, covering different batches, different strengths, different sizes of the same container closure system, and, possibly in some cases, different container closure systems.

Mean kinetic temperature

A single derived temperature that, if maintained over a defined period of time, affords the same thermal challenge to a drug substance or drug product as would be experienced over a range of both higher and lower temperatures for an equivalent defined period. The mean kinetic temperature is higher than the arithmetic mean temperature and takes into account the Arrhenius equation.

When establishing the mean kinetic temperature for a defined period, the formula of J. D. Haynes (*J. Pharm. Sci.*, 60:927-929, 1971) can be used.

New molecular entity

An active pharmaceutical substance not previously contained in any drug product registered with the national or regional authority concerned. A new salt, ester, or non-covalent-bond derivative of

an approved drug substance is considered a new molecular entity for the purpose of stability testing under this guidance.

Pilot scale batch

A batch of a drug substance or drug product manufactured by a procedure fully representative of and simulating that to be applied to a full production scale batch. For solid oral dosage forms, a pilot scale is generally, at a minimum, one-tenth that of a full production scale or 100,000 tablets or capsules, whichever is the larger.

Primary batch

A batch of a drug substance or drug product used in a formal stability study, from which stability data are submitted in a registration application for the purpose of establishing a re-test period or shelf life, respectively. A primary batch of a drug substance should be at least a pilot scale batch. For a drug product, two of the three batches should be at least pilot scale batch, and the third batch can be smaller if it is representative with regard to the critical manufacturing steps. However, a primary batch may be a production batch.

Production batch

A batch of a drug substance or drug product manufactured at production scale by using production equipment in a production facility as specified in the application.

Re-test date

The date after which samples of the drug substance should be examined to ensure that the material is still in compliance with the specification and thus suitable for use in the manufacture of a given drug product.

Re-test period

The period of time during which the drug substance is expected to remain within its specification and, therefore, can be used in the manufacture of a given drug product, provided that the drug substance has been stored under the defined conditions. After this period, a batch of drug substance destined for use in the manufacture of a drug product should be re-tested for compliance with the specification and then used immediately. A batch of drug substance can be re-tested multiple times and a different portion of the batch used after each re-test, as long as it continues to comply with the specification. For most biotechnological/biological substances known to be labile, it is more appropriate to establish a shelf life than a re-test period. The same may be true for certain antibiotics.

Semi-permeable containers

Containers that allow the passage of solvent, usually water, while preventing solute loss. The mechanism for solvent transport occurs by absorption into one container surface, diffusion through the bulk of the container material, and desorption from the other surface. Transport is driven by a partial-pressure gradient. Examples of semi-permeable containers include plastic bags and semi-rigid, low-density polyethylene (LDPE) pouches for large volume parenterals (LVPs), and LDPE ampoules, bottles, and vials.

Shelf life (also referred to as expiration dating period)

The time period during which a drug product is expected to remain within the approved shelf life specification, provided that it is stored under the conditions defined on the container label.

Specification

See Q6A and Q6B.

Specification – Release

The combination of physical, chemical, biological, and microbiological tests and acceptance criteria that determine the suitability of a drug product at the time of its release.

Specification - Shelf life

The combination of physical, chemical, biological, and microbiological tests and acceptance criteria that determine the suitability of a drug substance throughout its re-test period, or that a drug product should meet throughout its shelf life.

Storage condition tolerances

The acceptable variations in temperature and relative humidity of storage facilities for formal stability studies. The equipment should be capable of controlling the storage condition within the ranges defined in this guideline. The actual temperature and humidity (when controlled) should be monitored during stability storage. Short term spikes due to opening of doors of the storage facility are accepted as unavoidable. The effect of excursions due to equipment failure should be addressed, and reported if judged to affect stability results. Excursions that exceed the defined tolerances for more than 24 hours should be described in the study report and their effect assessed.

Stress testing (drug substance)

Studies undertaken to elucidate the intrinsic stability of the drug substance. Such testing is part of the development strategy and is normally carried out under more severe conditions than those used for accelerated testing.

Stress testing (drug product)

Studies undertaken to assess the effect of severe conditions on the drug product. Such studies include photostability testing (see ICH Q1B) and specific testing on certain products, (e.g., metered dose inhalers, creams, emulsions, refrigerated aqueous liquid products).

Supporting data

Data, other than those from formal stability studies, that support the analytical procedures, the proposed re-test period or shelf life, and the label storage statements. Such data include (1) stability data on early synthetic route batches of drug substance, small scale batches of materials, investigational formulations not proposed for marketing, related formulations, and product presented in containers and closures other than those proposed for marketing; (2) information regarding test results on containers; and (3) other scientific rationales.

4. REFERENCES

ICH Q1B: *"Photostability Testing of New Drug Substances and Products"*

ICH Q1C: *"Stability Testing of New Dosage Forms"*

ICH Q3A: *"Impurities in New Drug Substances"*

ICH Q3B: *"Impurities in New Drug Products"*

ICH Q5C: *"Stability Testing of Biotechnological/Biological Products"*

ICH Q6A: *"Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances"*

ICH Q6B: *"Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Biotechnological/Biological Products"*

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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	Thor B. Nielsen
Attorney Docket Number	PAC/20632 US (4137-04700)

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	3	5658919		1997-08-19	Ratnaraj, et al.	
	4	6319513	B1	2001-11-20	Dobrozsi	
	5	7776315	B2	2010-08-17	Pairet, et al.	
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	1	10152369	DE	A1	2002-05-08	Boehringer Ingelheim Pharma		☐
	2	9746243	WO	A1	1997-12-11	The Procter & Gamble Company		☐
	3	2003244799	AU	B2	2003-12-31	Cipla Limited		☐
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	1	Foreign communication from a related counterpart application - CA2,489,427, Examination Report, June 18, 2010, 3 pages.	☐
	2	Foreign communication from a related counterpart application - CA2,489,427, Examination Report, March 24, 2011, 2 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	Foreign communication from a related counterpart application - Notice of Intent to Grant, EP Application 03738280.1, October 23, 2008, 6 pages.	☐
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	23	Duonase Data Sheet, "The Complete Rhinitis Control," 6 pages, Cipla Limited, Mumbai, India.	☐
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	Attorney Docket Number	PAC/20632 US (4137-04700)

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Signature	/Rodney B. Carroll/	Date (YYYY-MM-DD)	2011-08-16
Name/Print	Rodney B. Carroll	Registration Number	39,624

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

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Application Number:	10518016
International Application Number:	
Confirmation Number:	4912
Title of Invention:	Combination of azelastine and steroids
First Named Inventor/Applicant Name:	Amar Lulla
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: 4912
LULLA *et al.*	Art Unit: 1616
Appl. No. 10/518,016	Examiner: Nielsen, Thor B.
Filed: July 6, 2005	Atty. Docket: PAC/20632 US (4137-04700)
For: **Combination Of Azelastine And Steroids**	

Declaration of Mr. Nikhil Chopra Under 37 C.F.R. § 1.132

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

Sir:

1. I, Mr. Nikhil Chopra (M.Sc.), hereby declare and state as follows:

2. I am currently employed by Cipla Limited ("Cipla"), the assignee of the above-referenced U.S. Application No. 10/518,016 (the '016 application).

3. I hold the degree of M. Sc. from University School of Science, Ahmedabad, India. A recent copy of my Curriculum Vitae, accurately listing my scientific credentials and work experience, is attached herewith as Exhibit A.

4. As stated in my Curriculum Vitae, I have been employed by Cipla, since year 1996. I have served as Head, Marketing and Sales since April 2004, overseeing the marketing and sales of Cipla's products in India. As evidenced in my Curriculum Vitae, I have extensive experience in marketing and sales of medicinal products in India.

5. It is my understanding that the claims in the above-captioned patent application recite a pharmaceutical composition comprising azelastine or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, and a pharmaceutically acceptable ester of fluticasone wherein the pharmaceutical formulation is

in a dosage form suitable for nasal administration (the "claimed composition"). Duonase®, a commercial embodiment of the claimed composition sold in India, is a metered spray formulation product for intranasal administration which contains 0.1% azelastine hydrochloride and 0.0357% fluticasone propionate and is indicated for the management of symptoms of allergic rhinitis and non-allergic vasomotor rhinitis.

6. Duonase® was launched in April 2004. Based on my education and experience, I am knowledgeable about the market share and sales history for Duonase® over the past seven years.

7. For at least the reasons discussed herein, it is my opinion that the sales of Duonase®, relative to the sales of other subsequent and closely copied brand products mentioned below, indicates a level of commercial success for Duonase® that supports the non-obviousness of the claimed composition.

8. Duonase® has achieved widespread commercial success in India. Acceptance from the medical fraternity was enormous as the claimed combination unexpectedly provided both quick relief and sustained control. Within a year of launch, we sold **167,826 units** of Duonase® across India and were the only company in the market selling the claimed composition.

9. Looking at the acceptance and success of the combination, the very next year in 2005, two more companies, Zydus Cadila and Sun Pharma, ventured into the market with their own similar brands of combination intranasal fluticasone propionate/azelastine hydrochloride products, Combinase AQ and Nezalast, respectively.

10. Recognizing the success of the claimed composition, additional companies have entered the market on almost a yearly basis, with 1 entry in 2006 (Azeflo by Lupin Ltd), 1 entry in 2007 (Azenate by Entod), 1 entry in 2009 (Sarnase by Ranbaxy), and 2 entries in 2010 (Ezicas-AZ by Intas Pharma and Nasocom-AZ by Dr. Reddy's Labs).

11. A description of some of the competitive products is provided in Table 1 and a summary of the sales for Duonase® and the competitive products is provided in Table 2. All facts and figures taken for sales analysis are from IMS Health Information and Consulting Services India Pvt. Ltd., ICC Chambers II, 4th Floor, Near Saki Vihar Telephone Exchange, Saki-Vihar Road, Powai, Mumbai 400702, India. Website: www.imshealth.com.

Table 1

Brand	**Composition**	**Company**	**Dose**
Duonase	Fluticasone Propionate IP….0.0357 % w/v, Azelastine Hydrochloride BP….0.10 % w/v Benzalkonium Chloride IP…0.01 % w/v (As preservative) Phenyl Ethyl Alcohol USP….0.25 % v/v (As preservative)	**Cipla**	**70 M.D**
Azeflo	Fluticasone Propionate IP….0.05 % w/v, Azelastine Hydrochloride BP….0.14 % w/v Benzalkonium Chloride Solution IP…0.02 % w/v (As preservative) Phenyl Ethyl Alcohol USP….0.25 % w/v (As preservative) Excipients……q.s.	Lupin	70 MD
Nazomac AF	Fluticasone Propionate IP….0.05 % w/v, Azelastine Hydrochloride BP….0.14 % w/v Preservatives: Benzalkonium Chloride IP…0.01 % w/v	Macleods	120 MD

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	Phenyl Ethyl Alcohol USP….0.25 % w/v Excipients……..….q.s.		
Combinase AQ	Fluticasone Propionate IP….0.05 % w/v, Azelastine Hydrochloride BP….0.14 % w/v Preservatives: Benzalkonium Chloride Solution IP…0.02 % w/v Phenyl Ethyl Alcohol USP….0.25 % w/v Excipients……..….q.s.	Zydus Cadila	70 MD
Nasocom AZ	Fluticasone Propionate IP….0.05 % w/v, Azelastine Hydrochloride BP….0.14 % w/v Preservatives: Benzalkonium Chloride IP…0.01 % w/v Phenyl Ethyl Alcohol USP…0.25 % w/v Excipients……..….q.s.	DRL	70 M.D
Duospray	Fluticasone Propionate IP….0.05 % w/v, Azelastine Hydrochloride BP….0.14 % w/v Preservatives: Benzalkonium Chloride Solution IP…0.02 % w/v Phenyl Ethyl Alcohol USP….0.25 % w/v Excipients……..….q.s.	Emcure	70 M.D

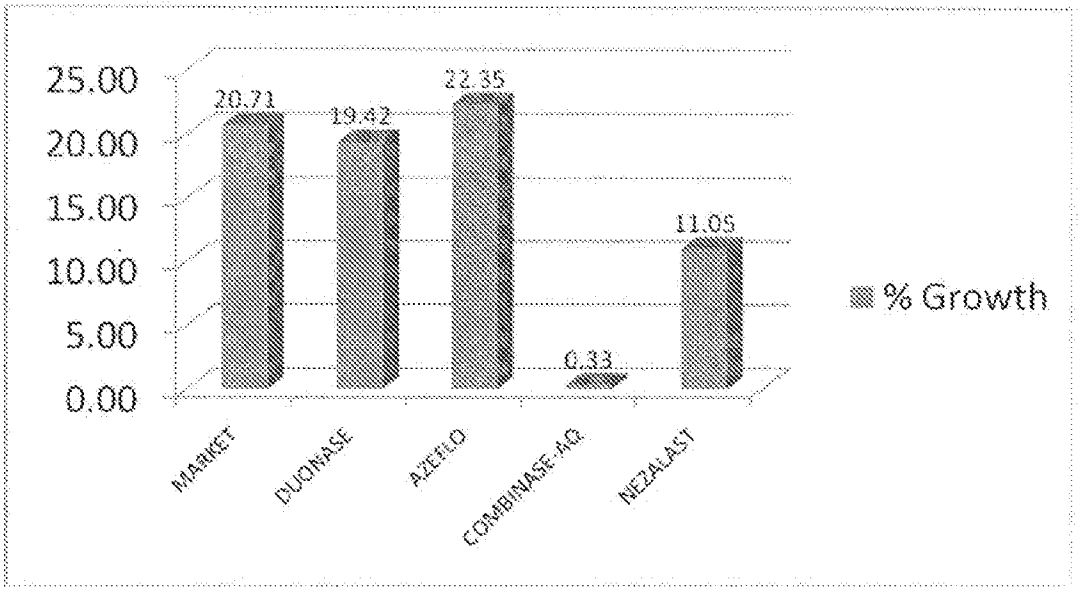
Table 2

PRODUCT DESC		LAUNCH	MAT ~ 03/2005	MAT ~ 03/2006	MAT ~ 03/2007	MAT ~ 03/2008	MAT ~ 03/2009	MAT ~ 03/2010	MAT ~ 03/2011
	COMPANY		UNITS	UNITS	UNITS	UNITS	UNITS	UNITS	UNITS
SELECTED TOTAL			167,826	254,972	348,373	545,163	633,464	771,417	918,920
DUONASE	CIPLA	200404	167,826	240,271	263,680	350,072	398,499	439,257	511,426
COMBINASE-	ZYDUS CADILA*	200510	0	11,279	47,041	87,583	90,553	146,429	145,219

AQ									
NEZALAST	SUN PHARMA*	200511	0	3,422	19,830	36,418	43,069	52,794	60,360
AZEFLO	LUPIN LIMITED	200606	0	0	17,822	69,301	97,416	129,850	160,091
AZENATE	ENTOD	200707	0	0	0	1,789	3,927	1,747	2,503
SARNASE	RANBAXY*	200909	0	0	0	0	0	1,340	220
EZICAS-AZ	INTAS PHARMA*	201004	0	0	0	0	0	0	23,514
NASOCOM-AZ	DR REDDYS LABS	201006	0	0	0	0	0	0	15,587

12. As shown in Table 2, the overall market for the claimed composition has grown steadily from 167,826 units reported in 2005 to 918,920 units reported in 2011. The growth of the market is further represented in Fig. 1, which indicates that the overall market for the claimed composition has grown at a rate of 20.71%. Also as shown in Figure 1, Duonase® has grown at about the same rate, 19.42%, and the overall market, 20.71%.

Fig. 1



13. As shown in Figs. 2 and 3, Duonase® has remained the single largest participant in the market since inception in 2004.

Fig. 2

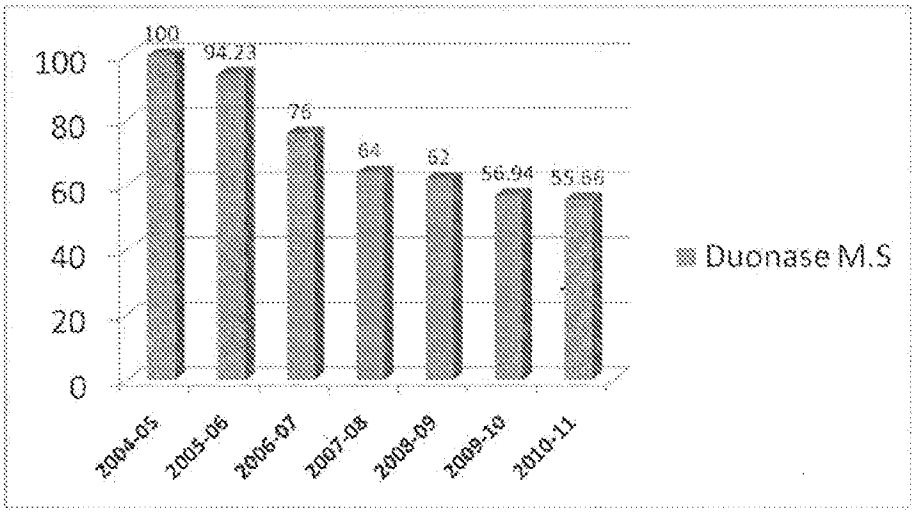
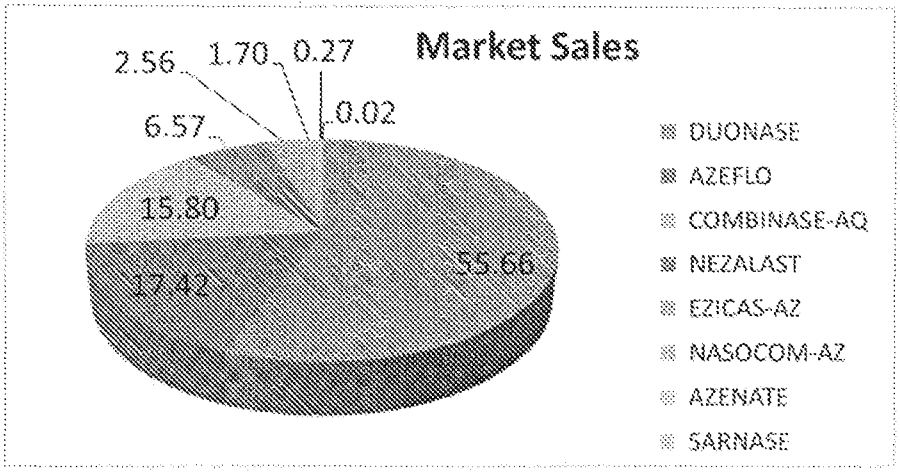


Fig. 3



14. Based upon this information and my personal experience, it is my opinion that the commercial success for Duonase® as demonstrated by the growth of the overall market since creation by Cipla, the continued growth of sales for Duonase®, and the rapid, wide-spread, and on-going copying by competitors supports the non-obviousness of the claimed composition.

15. I further state that all statements made on my own knowledge are true and that all statements made on information and belief are believed to be true and further that willful false statements and the like are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the U.S. Code and may jeopardize the validity of the application or any patent issuing thereon.

12/08/2011
Date

Mr. Nikhil Chopra

Exhibit A

CURRICULUM VITAE

Name	:	Nikhil Chopra
Father's Name	:	Ashok Kumar Chopra
Current Address	:	No.301, 3rd floor, Orchid, Dosti Acres New Uphill Link Road, Off S M Road Wadala (East), Mumbai : 400 037.
Date of birth	:	01 October, 1973
Telephone	:	9820702192 (M)
Email	:	nikhil73@gmail.com
Educational Qualification	:	M.Sc. from University School of Science, Ahmedabad (1996) B.Sc. from Bhavans College, Ahmedabad, (1994) H.Sc. from Amrut High School, Ahmedabad, (1991) S.S.C. from Rachana High School, Ahmedabad (1989) Advance Diploma in Computer Application (ADCA)
Accolades	:	Awarded three gold medals at Third B.Sc. (Chem) Gujarat University Exam 1994
Work Experience	:	15 years of experience at Cipla Ltd (YOJ : 1996)
Current position	:	Head Maketing and Sales, Cipla Ltd, Mumbai, India

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Amar Lulla, *et al.*	§ Confirmation No.:	4912
Serial No.:	10/518,016	§ Group Art Unit:	1616
Filed:	July 6, 2005	§ Examiner:	Nielsen, Thor B.
For:	COMBINATION OF AZELASTINE AND STEROIDS	§ Attorney Docket:	PAC/20632 US (4137-04700)

DECLARATION OF GEENA MALHOTRA UNDER 37 CFR § 1.132

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

Sir:

1. I, Geena Malhotra, hereby declare and state as follows:

2. I am currently employed by Cipla Limited ("Cipla"), the assignee of the above-referenced U.S. Pat. App. No. 10/518,016 (the '016 application), as Head of Research and Development.

3. I hold the degree of B. Pharm. from SNDT University. A copy of my *Curriculum Vitae*, accurately listing my scientific credentials and work experience, is attached herewith as Exhibit A.

4. I am a co-inventor of the invention claimed in the '016 application.

5. I have been informed that the U.S. Patent Office has cited published European Pat. App. Publication No. 0780127A1 by Ronald Cramer ("*Cramer*") as prior art against the '016 application, and specifically that the U.S. Patent Office considers Example 3 of *Cramer* to be the closest prior art example.

6. I have reviewed and am familiar with *Cramer*, and Example 3 of *Cramer* has been reproduced experimentally under my supervision. For at least the reasons discussed in detail below, the formulation described in Example 3 of *Cramer* is inoperable and unacceptable as a pharmaceutical formulation in a dosage form suitable for nasal administration.

7. Example 3 of Cramer was reproduced according to the following table of ingredients and process of preparation:

Ingredients	**Quantity (% w/v)**
Drugs (Azelastine hydrochloride + Triamcinolone acetonide)	98 mcg (0.07%) + 70 mcg (0.05%)
Hydroxy propyl methyl cellulose [HPMC (E4M)]	1.0
Glycerin	2.0
Polysorbate 80	0.05
Benzalkonium Chloride NF	0.02
Disodium EDTA	0.05
Sodium Chloride	0.9
Purified water	q.s. to vol.

Process of preparation:

1) Part quantity of purified water was taken in a vessel.
2) Sodium chloride and Disodium EDTA was added and dissolved under stirring followed by heating the bulk.
3) Hydroxy propyl methyl cellulose (HPMC) was added and dispersed under stirring.
4) Stirring was done and bulk was held at 2-8°C overnight.
5) Glycerin was added and mixed in above bulk under stirring.
6) Part quantity of purified water was taken and Azelastine hydrochloride was dissolved in it to form drug slurry.
7) Drug slurry of step # 6 was added in main bulk of step # 5 under stirring.
8) Polysorbate 80 was added and dissolved in part quantity of purified water. Triamcinolone acetonide was added to this solution under stirring.
9) Drug slurry of step # 8 was added in above bulk of step # 7 under stirring.

10) Benzalkonium chloride was added in part quantity of purified water and this solution was added in above bulk under stirring.

11) Volume was made-up with purified water.

12) Stirring was done and pH was checked.

8. Upon completion of the process of preparation, the following observations were noted:

Stability test:	**Azelastine hydrochloride + Triamcinolone acetonide Nasal Spray**
	INITIAL OBSERVATIONS
Product description	White, translucent, viscous suspension. On keeping, the active ingredient settled in bottle and was very difficult to re-disperse. This is expected to lead to variation in content per spray. A lot of foam was generated on shaking which was difficult to dissipate owing to high viscosity; this is expected to lead to inconsistent delivery.
Osmolality	554 mOsm/kg (***Hyperosmotic/hypertonic***)
Product performance with 40 mcl nasal pump and suitable actuator	After actuation of nasal pump, ***bulk was discharged as a Jet (a stream of liquid forcefully shooting forth from the orifice) and not as a Spray.***

9. From the observations set forth in paragraph 8, it is conclusive that the formulation described in Example 3 of *Cramer* is inoperable and unacceptable as a pharmaceutical formulation in a dosage form suitable for nasal administration for at least the following reasons:

(A) Unacceptable settling and difficulty in resuspending – homogeneity of the active material in product is not expected to be maintained due to caking seen at the bottom of vial of the formulation;

(B) Unacceptable jet rather than desired spray mist – after actuation of the nasal pump, the product comes out as jet (a stream of liquid forcefully shooting forth from the orifice) and not a spray (a mist of fine liquid particles), and due to which the drug is not expected to be suitably deposited on nasal mucosa; and

(C) Unacceptable osmolality – It is widely known and accepted that nasal sprays are preferably isotonic (as is acknowledged by *Cramer* at page 3, lines 8 and 49) rather than hypertonic.[1] Accordingly, the undesirable hyperosmotic (i.e., 554 mOsm/kg), hypertonic character of the product is expected to give rise to irritation of the nasal mucosa.

10. Insofar as the azelastine hydrochloride + triamcinolone acetonide formulation of Example 3 of *Cramer* was found to be inoperable and unacceptable as a pharmaceutical formulation in a form suitable for nasal administration, no appropriate comparison can be made between *Cramer's* Example 3 formulation and the formulation of the claimed invention. In addition, any further proposed chemical analysis or stability studies would yield no data relevant to any such comparison.

11. 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: 12th Aug' 2011

Geena Malhotra

[1] "[I]sotonic conditions are required for ophthalmic, nasal, most electrolyte and other preparations." A hypertonic solution will cause water to leave the intracellular compartment with consequent cell shrinkage while a hypotonic solution will cause the cell to imbibe water which produces swelling, distention and finally rupture of the cells. (*See Inorganic Medicinal and Pharmaceutical Chemistry, Block, Roche et al; 1986, pg-100*, attached hereto as Exhibit B). Further specifically with reference to nasal formulations, shrinkage of epithelial cells has been observed in the presence of hypertonic solutions. Hypertonic saline solutions also inhibit or cease ciliary activity *(See Development of Nasal Delivery Systems: A Review, Drug Development and Delivery, Vol. 2 No. 7, October 2002*, attached hereto as Exhibit C).

Exhibit A

CURRICULUM VITAE

Name	Mrs. Geena Malhotra
Date of Birth	April 20, 1964
Residential address	4, Anderson House Opposite Mazgaon Dock Post Office, Mazgaon, Mumbai-10 India Tel: 91 22 23720714
Educational Qualification	B. Pharm. (1985) SNDT University
Work experience	
1986 -1991	R&D Scientist at Cipla Ltd., Mumbai Central
1991 – 1995	Group leader formulation development, Cipla Ltd., Mumbai Central
1995 onwards and Current position	Head – Research & Development
International Seminars	Nov. 1995 : Attended International seminar on IPEC, France
	Apr. 1997 : Attended Eudragit workshop by 'Rohm Pharma' Germany
	June 1998 : Attended Annual Conference on Dry Powder Inhalers, U.K
	June 2000 : Attended Annual Conference on Dry Powder Inhalers, U.K
	June 2001 : Attended Annual Conference on Dry Powder Inhalers, U.K
	Aug. 2001 : Attended Alginate and coating training, Belgium
	Nov. 2001 : Attended International seminar on Nutrition labeling and health claim, Mumbai
	June 2002 : Attended Annual Conference on Dry Powder Inhalers, U.K

May 2005 : Attended RDD Conference, Paris, France

May 2006 : Attended RDD Conference, Florida, USA & presented a Poster Presentation on Zerostat V – A Non-Electrostatic Valved Holding Chamber

Mar 2007 : Attended 1st International Symposium on Hot Melt Extrusion, Frankfurt, Germany

June 2008 : Attended Leistritz Pharmaceutical Extrusion Seminar, USA

March 2010: Attended Lipid Symposium, Singapore

April 2010 : Attended RDD Conference, Florida, USA

June 2010 : Attended Gerteis Seminar, Switzerland

October 2010: Attended CPhi Conference, Paris, France

May 2011 : Attended Interpack 2011, Germany

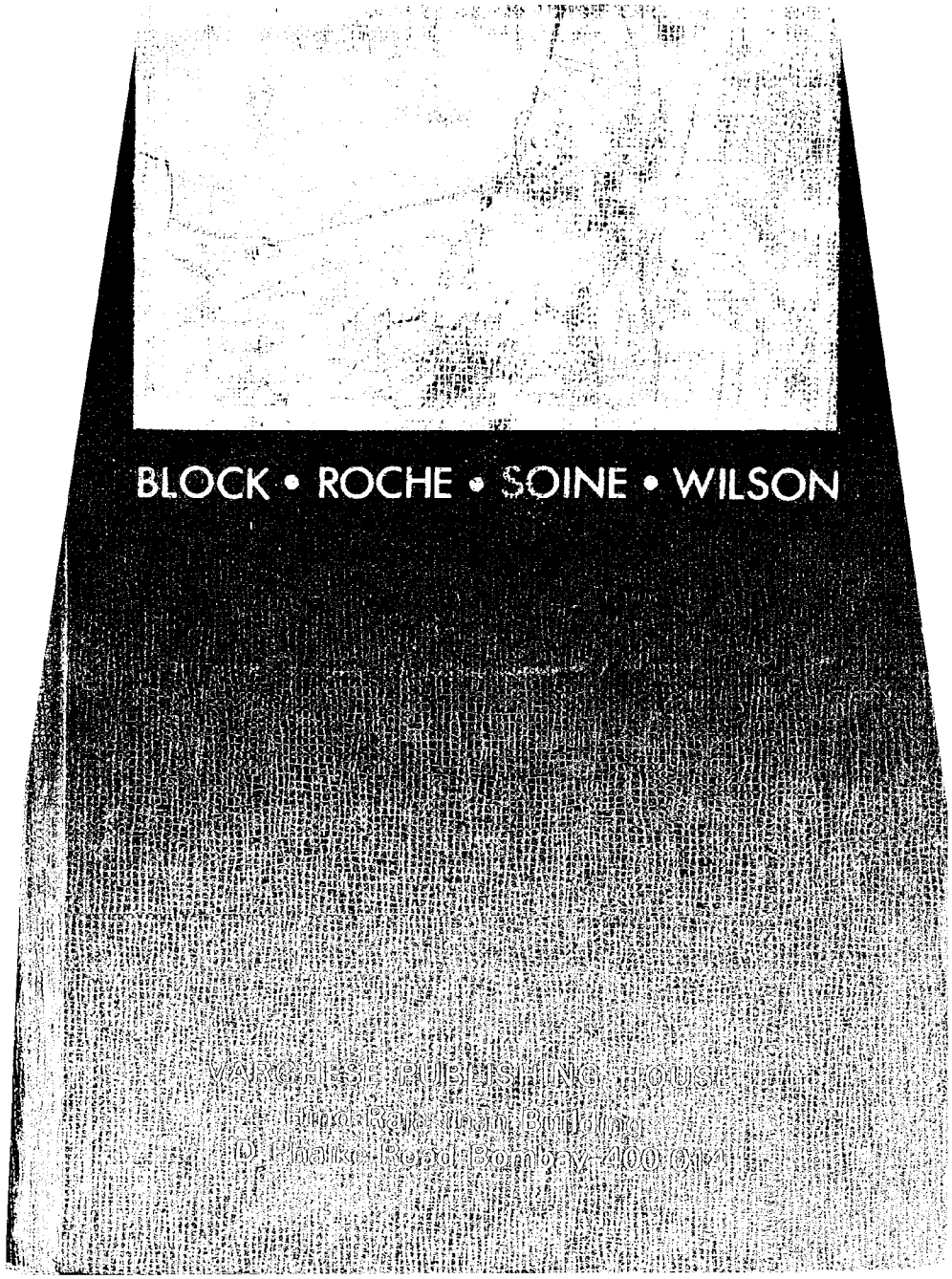
Inventor of following patents and applications

1. Cyclosporine Formulations (AU706995).
2. Benzimidazole pharmaceutical composition and process of preparation (WO9852564); Granted in GB (GB2343117).
3. Topical sprays (WO00/45795).
4. A pharmaceutical composition containing Bisphosphonic acid(s) or salt(s) thereof and a process for preparing thereof (WO01/32185).
5. Spacer device for Inhaler (WO0033902); Granted in Europe, US & Canada.
6. Anti-wrinkle cream composition (IN182970).
7. Herbal antiseptic cream composition (ZA98/03753).
8. Topical Medicinal spray composition and their preparation which compositions can be used to treat a variety of disorders (IN188096).
9. Process for the manufacture of metered dose topical aerosol topical aerosol dispenser as spray (93/BOM/99).
10. A spacer device for administering orally a volatile liquid composition by inhalation (IN190657).
11. Oil-in water micro emulsion (EP0760237A1).

12. Pharmaceutical formulation including a suspension of Cefadroxil (ZA2000/7740).
13. An improved device for administering orally or nasally the powdered or volatile composition by inhalation (IN188288); Granted in South Africa & Sri Lanka.
14. Bilayered tablet containing Lamivudine, Stavudine & Nevirapine (ZA2001/10499)
15. Tablet containing Lamivudine, Zidovudine & Nevirapine (ZA2001/10500).
16. Tablet containing Lamivudine and Stavudine (ZA2001/10501).
17. Tablet containing Lamivudine, Stavudine and Nevirapine (ZA2001/10502).
18. Anti malarial Compositions and Process Thereof (WO2005/023304); Granted in Seychelles & South Africa.
19. A Pharmaceutical Composition Containing Bisphosphonic Acid(S) Or Salt(S) Thereof and a Process of Preparing Thereof (WO2005/030177); Granted in South Africa.
20. A Process For Preparing A Topical Medicinal Spray Composition (IN188096).
21. Anti-Histaminic Composition (W02006/008512); Granted in Morocco, Iran, Bangladesh, OAPI and South Africa.
22. Enteric Coated Formulation For Bisphosphonic Acids And Salts Thereof (US6676965).
23. Inhalation Formulations (W02005/087192); Granted in Morocco & OAPI.
24. Inhaler (W02006/051300); Granted in Morocco & Singapore.
25. Medicament Inhaler Device (W02005/113043); Granted in Burundi, Lebanon, Malta, Myanmar & Iran.
26. Medicated Stick Composition (WO0044347).
27. Multi-dose inhaler (WO2005004962); Granted in Lebanon, Malta, Morocco, Syria, Singapore, Eurasia, South Africa & US.
28. Oral formulations for 5-HT- Receptor agonists, uses and methods of treatment employing the same (WO 2005/044222); Granted in Morocco, South Africa & UK.
29. Pharmaceutical Combinations and Formulations With Improved stability (W02005/011737).
30. Pharmaceutical Combinations Comprising Lamivudine, Stavudine And Efavirenz For Treating viral Infections (WO2004089383 / WO2004089382).
31. Pharmaceutical Composition (WO2004/071398).
32. Pharmaceutical Composition Comprising A Betaminetic Agent And A Mucolytic Agent (W02006/030221).
33. Pharmaceutical Composition Comprising An Isomer Of A Betamimetic Agent And An Anti- Cholinergic Agent (W02006/027595).

34. Pharmaceutical Composition Comprising Azelastine And Steroid (WO2003/105856); Granted in Europe, Morocco, GB, Algeria, Singapore, South Africa & New Zealand.
35. Pharmaceutical Composition Comprising Immunosuppressants for the Treatment Of Dermatophytosis (WO2004/071510).
36. Pharmaceutical Composition Comprising Tibolone And Process for Producing The Same (WO2005/117899).
37. Pharmaceutical Composition for the Administration of Water-Insoluble pharmaceutically active substances and a process for preparation thereof (WO0132143).
38. Pharmaceutical Compounds & Composition (WO2006/064283).
39. Pharmaceutical dispensing aid (WO2005/000712).
40. Pharmaceutical Formulation Comprising Anti-Obesity Agent and Acidulant (WO2004096202).
41. Pharmaceutical formulation with improved stability (EP1680092 A2).
42. Pharmaceutical Formulations Comprising A Proton Pump Inhibitor (WO2005/000269).
43. Pharmaceutical Formulations Comprising Beta-2 Adrenoreceptor Agonists and Xanthines (W02004/050067).
44. Pharmaceutical Inclusion Complexes Containing a Steroid and Optionally an Antibacterial Agent (WO2004/069280).
45. Pharmaceutical Preparation Comprising Calcitonin (GB2417202 A).
46. Pharmaceutical Product Comprising a Beta-2 Adrenergic Agonist And An H 1-Receptor Antagonist (WO2005/041969).
47. Pharmaceutical Product Comprising a Beta-2 Adrenoceptor Agonist and an Antihistamine (WO2005/007145).
48. Pharmaceutical Products and Composition Comprising Specific Anticholinergic Agents, Beta-2 Agonists and Corticosteroids (ZA200501703).
49. Proton Pump Inhibitor Composition In Paste Form (GB2394895 A).
50. Sterilization Process (US2005201888).
51. Topical immunotherapy and compositions for use therein (US2006204446).
52. Topical Spray Compositions (US6962691, EP1150661).
53. Transdermal pharmaceutical formulation (WO 2005/041943); Granted in Bangladesh, Burundi, Haiti, Malta, Morocco, Panama, Peru, South Africa & Singapore.
54. Venlafaxine Hydrochloride extended release pellets (KR20060065319)
55. Omeprazole (WO98/52564).
56. Medicated stick composition (WO0044347).

57. Pharmaceutical compositions containing new polymorphic forms of Olanzapine & uses thereof (US7022698, EP1246827).
58. Inhalation device (ZA98/11257).
59. Anti-wrinkle cream composition (IN182970).
60. Improved Dry Powder Inhaler (WO2007/144659).
61. Antiretroviral Solid Oral Composition (PCT/GB2007/003061).
62. A pharmaceutical composition (WO2007/026156).
63. Anti-malarial composition (PCT/GB2006/002919).
64. Pharmaceutical Formulation (WO2008/102128).
65. Multidose Inhaler (WO2008/114034).
66. Pharmaceutical combinations (WO 2007/068934).
67. Pharmaceutical composition (WO 2007/072060).
68. Stable formulations for Inhalations (PCT/GB08/002029).
69. Pharmaceutical Compositions (PCT/GB2008/002567).
70. Solid Pharmaceutical Composition (PCT/GB2008/003155).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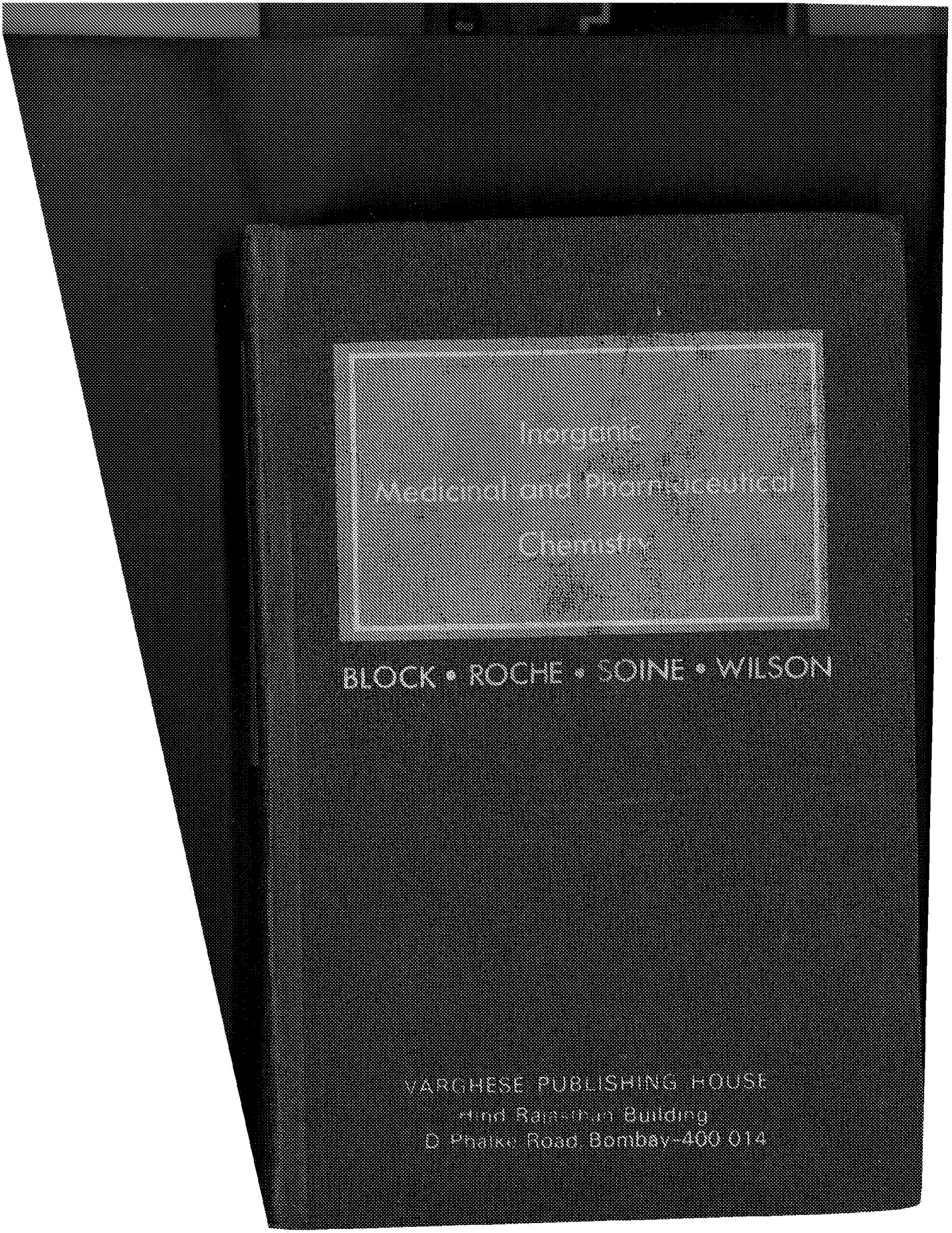
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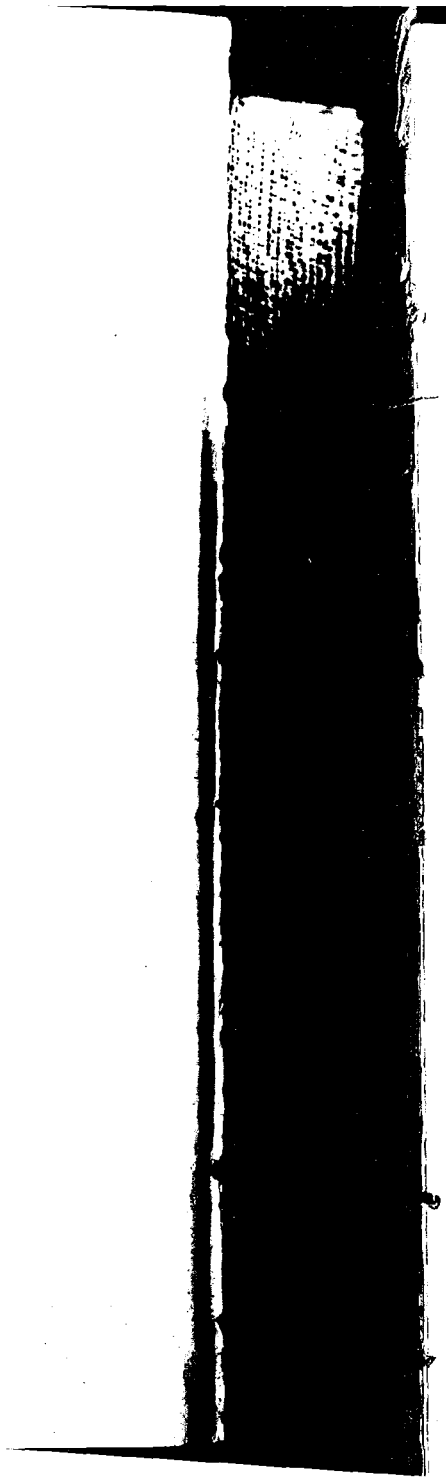

Inorganic Medicinal and Pharmaceutical Chemistry

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INDIAN EDITION

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Preface

Inorganic Medicinal and Pharmaceutical Chemistry has been designed as a classroom textbook written with two purposes in mind. The first is to present a review of those principles of inorganic chemistry that apply to medicinal and/or pharmaceutical chemistry. In that regard, the first two chapters are devoted to explanations of atomic structure as it relates to bonding forces and complexation, and a summary of the important physical properties of each element group from the periodic table. The second purpose is to present detailed discussions of those inorganic agents used as pharmaceutical aids and necessities or as therapeutic and diagnostic agents. Those products used as pharmaceutical aids and necessities include acids and bases, buffers, antioxidants, water, and selected tableting aids. Inorganic compounds used therapeutically include products containing fluid/electrolytes, biochemically important ions, and therapeutically important ions. Other inorganic products described are antacids, cathartics, topical agents, dental products, inhalants, antidotes, etc. Radiopharmaceuticals are discussed both as diagnostic and as therapeutic agents. The toxicity problems associated with some of the inorganic cations are reviewed.

The general format is to define the class of products under discussion, to describe the rationale for their use, and then to discuss the specific agents. The latter usually includes the official description of the product, contraindications, therapeutic and pharmaceutical incompatibilities where appropriate, the official use, and, in many cases, alternate uses. Pertinent references have been provided.

Those who have taught inorganic pharmaceutical chemistry will note the occasional use of an illustration and some of the text from the eighth edition of *Rogers' Inorganic Pharmaceutical Chemistry*. However, the clinical emphasis in pharmacy education requires that topics be regrouped away from a chemical classification and classified according to their use. Selected chapters can be used as needed depending on where material is presented in a school's curriculum. Those schools using courses in intro-

Such solutions are termed *isotonic*, indicating that their effect on *cellular tone, tonicity*, is the same as that of normal physiological fluids. In other words, isotonic solutions have osmotic pressures equal to the osmotic pressure of intracellular fluid ($\pi_{soln} = \pi_{cell}$). These solutions can be applied to tissues or injected without causing damage to cells through osmotic effects.

The effect on cells of nonisotonic solutions follows the physical description of osmotic pressure imbalance mentioned above. If the osmotic pressure of the applied solution is greater than that of the intracellular fluid, the solution is termed *hypertonic* ($\pi_{soln} > \pi_{cell}$). This type of solution will cause water to leave the intracellular compartment with consequent cell shrinkage, a phenomenon known as *plasmolysis* (the term *crenation* is applied to this occurrence in red blood cells).

The opposite situation, in which the osmotic pressure of the solution is less than that of the intracellular fluid, results in a *hypotonic* solution ($\pi_{soln} < \pi_{cell}$). When a solution of this type comes into contact with tissue cells, the cell will imbibe water, which produces swelling, distention, and finally rupture. This course of events is referred to as *plasmoptysis*, or *hemolysis* in the case of red blood cells.

Hypotonic or hypertonic solutions are sometimes used to advantage in electrolyte therapy (see Chapter 5), and the production of hypertonic conditions in kidney tubules and the intestinal tract is responsible for the action of osmotic diuretics and saline cathartics, respectively (see Chapter 8). However, isotonic conditions are required for ophthalmic, nasal, most electrolyte, and other preparations.

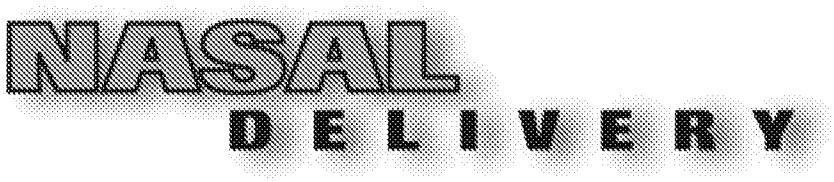
Experimental evidence (e.g., freezing point data) shows that a 0.9% w/v aqueous solution of sodium chloride is isotonic with all body fluids (including lachrymal fluid). Since sodium chloride is normally found in extracellular fluid, it follows that this salt can be used as the compound of choice for the adjustment of tonicity. Comparisons of the freezing point depression of various drugs with that of sodium chloride have resulted in the development of *sodium chloride equivalents*. These are factors which, when multiplied by the weight of a corresponding compound, provide a number equivalent to the weight of sodium chloride necessary to produce a solution having the same tonicity, provided that the weight of the compound and the calculated weight of sodium chloride are dissolved in equal volumes of water. This procedure allows the quantity of sodium chloride being replaced in a particular solution by another compound to be determined as well as the amount of sodium chloride to be added to the preparation to make it isotonic on the basis of a 0.9% solution. Of course, hypotonic and hypertonic solutions having a particular tonicity relative to sodium chloride can be prepared using the same factors. A table of sodium chloride equivalents for some commonly used drugs and sample calculations are given in Appendix B.

Drug Delivery

Exhibit C

Issue Date: Vol. 2 No. 7 October 2002, Posted On: 3/28/2008

Development of Nasal Delivery Systems: A Review



In recent years, the nasal mucosa has been considered as an administration route to achieve faster and higher level of drug absorption. The richly supplied vascular nature of the nasal mucosa coupled with its high drug permeation makes the nasal route of administration attractive for many drugs, including proteins and peptides.[1] In addition, absorption of drug at the olfactory region of the nose provides a potential for a pharmaceutical compound to be available to the central nervous system. The nasal delivery of vaccines is another very attractive application in terms of efficacy and patient acceptance.[2]

The purpose of this review is to provide an overview of the factors that will affect formulation development and design of nasal products. The anatomical and physiological considerations of the nose, mechanism of nasal drug absorption and physicochemical factors affecting the formulation design will be presented. The role of absorption enhancers and target nasal drug delivery will also be discussed.

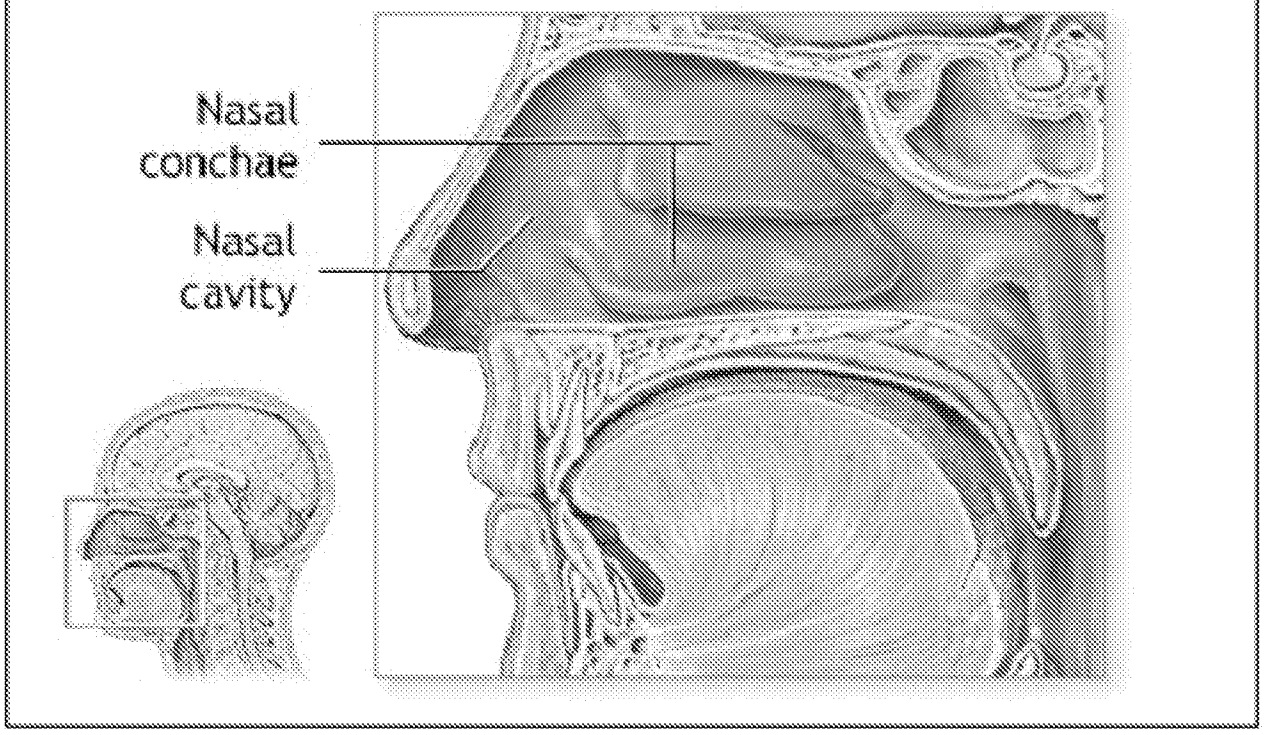
ANATOMY & PHYSIOLOGY OF THE NOSE

The nose is a complex organ from a kinetic point of view because three different processes: deposition, clearance or translocation and absorption of drugs take place inside the nose. For effective administration of therapeutic drugs through the nasal route, its anatomy and related physiological features must be taken into consideration.

The nasal septum divides the nasal cavity into two unequal cavities. The septum consists mostly of cartilage and skin, and therefore, the penetration of drugs is low. The most efficient area for drug absorption is the highly vascularized lateral wall of the nasal cavity: the mucosa lined over the turbinates or conchae (Figure 1).

FIGURE 1

Anatomy of the Nose



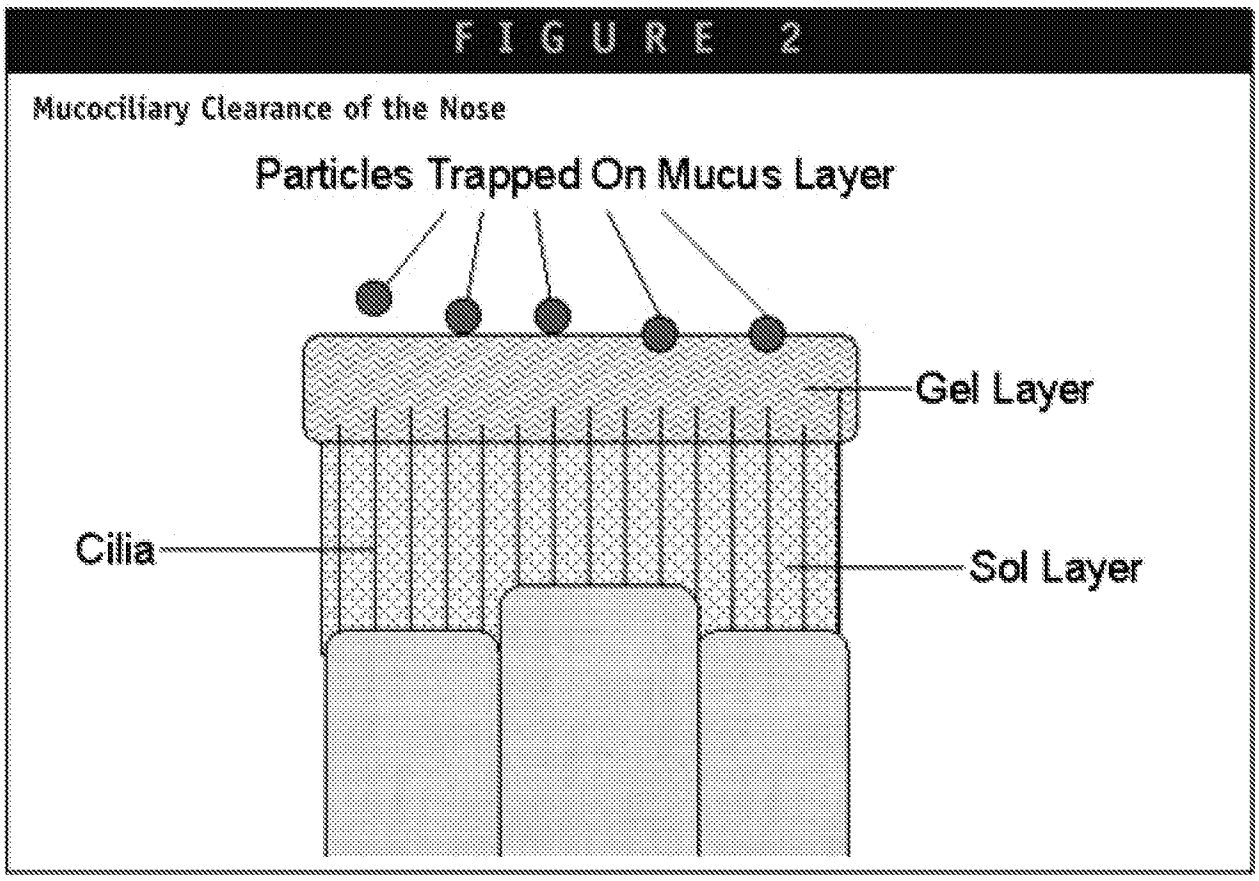
Effect of Deposition on Absorption

Deposition of the formulation in the anterior portion of the nose provides a longer nasal residence time. However, the anterior portion of the nose is an area of low permeability. On the other hand, depositing a drug in the posterior portion of the nose, where the drug permeability is generally higher, provides shorter residence time. The method of administration and properties of the formulation determine the deposition site.

Harris[3] compared the deposition and removal of metered dose sprays with nasal drops. Nasal sprays were deposited anteriorly, after which small portions were cleared slowly into nasal pharynx by mucociliary clearance. In contrast, drops were deposited mostly posteriorly and were removed rapidly in large portions into the nasal pharynx.

Effect of Mucociliary Clearance

It is important that the integrity of the nasal clearance mechanism is maintained to perform normal physiological functions such as the removal of dust, allergens and bacteria. The ciliary activity is the driving force of the secretory transport in the nose to constantly remove particles that are trapped on the mucus blanket during inhalation (Figure 2).



The absorption of drugs is influenced by the residence (contact) time between the drug and the epithelial tissue. The mucociliary clearance is inversely related to the residence time and therefore inversely proportional to the absorption of drugs administered. A prolonged residence time in the nasal cavity may also be achieved by using bioadhesive polymers, microspheres, chitosan or by increasing the viscosity of the formulation.

Nasal mucociliary clearance can also be stimulated or inhibited by drugs, excipients, preservatives and/or absorption enhancers and thus affect drug delivery to the absorption site.

Effect of Enzymatic Activity

Several enzymes that are present in the nasal mucosa might affect the stability of drugs. For example, proteins and peptides are subjected to degradation by proteases and amino-peptidase at the mucosal membrane. The level of amino-peptidase present is much lower than that in the gastrointestinal tract.[4] Peptides may also form complexes with immunoglobulin (Igs) in the nasal cavity leading to an increase in the molecular weight and a reduction of permeability.[5]

Nasal Emulsions & Ointments: Nasal emulsions and ointments have not been studied in detail as other nasal delivery systems. They offer advantages for local application mainly due to their viscosity. One of the major disadvantages is poor patient acceptability. The physical stability of emulsion formulations and precise delivery are some of the main formulation issues.

Specialized Delivery System: Microsphere technology is one of the specialized systems becoming popular for designing nasal products. Microspheres may provide more prolonged contact with the nasal mucosa and thus enhance absorption. Microspheres for nasal applications have been prepared using biocompatible materials, such as starch, albumin, dextran and gelatin.[9] Their toxicity/irritancy should be evaluated. It was hypothesized[10] that in the presence of starch microspheres, the nasal mucosa is dehydrated due to moisture uptake by the microspheres. This results in reversible "shrinkage" of the cells, providing a

temporary physical separation of the tight (intercellular) junctions that increases the absorption of drugs.

Drug Concentration, Dose & Dose Volume

Drug concentration, dose and volume of administration are three interrelated parameters that impact the performance of the nasal delivery performance. Nasal absorption of L- Tyrosine was shown to increase with drug concentration in nasal perfusion experiments.[7] However, in another study,[11] Aminopyrine was found to absorb at a constant rate as a function of concentration. In contrast, absorption of salicylic acid was found to decline with concentration. This decline is likely due to nasal mucosa damage by the permeant.

Formulation pH

The pH of a nasal formulation is important for the following reasons:

- To avoid irritation of nasal mucosa;
- To allow the drug to be available in unionized form for absorption;
- To prevent growth of pathogenic bacteria in the nasal passage;
- To maintain functionality of excipients such as preservatives; and
- To sustain normal physiological ciliary movement.

Lysozyme is found in nasal secretions, which is responsible for destroying certain bacteria at acidic pH.[12] Under alkaline conditions, lysozyme is inactivated and the nasal tissue is susceptible to microbial infection. It is therefore advisable to keep the formulation at a pH of 4.5 to 6.5 keeping in mind the physicochemical properties of the drug as drugs are absorbed in the un-ionized form.

Buffer Capacity

Nasal formulations are generally administered in small volumes ranging from 25 to 200 µL with 100 µL being the most common dose volume. Hence, nasal secretions may alter the pH of the administrated dose. This can affect the concentration of un-ionized drug available for absorption. Therefore, an adequate formulation buffer capacity may be required to maintain the pH in-situ.

Osmolarity

Drug absorption can be affected by tonicity of the formulation. Shrinkage of epithelial cells has been observed in the presence of hypertonic solutions. Hypertonic saline solutions also inhibit or cease ciliary activity. Low pH has a similar effect as that of a hypertonic solution.

Gelling/Viscofying Agents or Gel-Forming Carriers

According to a study by Pennington *et. al.*[13], increasing solution viscosity may provide a means of prolonging the therapeutic effect of nasal preparations. Suzuki *et. al.*[14]showed that a drug carrier such as hydroxypropyl cellulose was effective for improving the absorption of low molecular weight drugs but did not produce the same effect for high molecular weight peptides. Use of a combination of carriers is often recommended from a safety (nasal irritancy) point of view.

Solubilizers

Aqueous solubility of drug is always a limitation for nasal drug delivery in solution. Conventional solvents or co-solvents such as glycols, small quantities of alcohol, Transcutol (diethylene glycol monoethyl ether), medium chain glycerides and Labrasol (saturated polyglycolyzed C_8- C_{10} glyceride) can be used to enhance the solubility of drugs. Other options include the use of surfactants or cyclodextrins such as HP-ß-Cyclodextrin that serve as a biocompatible solubilizer and stabilizer in combination with lipophilic absorption enhancers. In such cases, their impact on nasal irritancy should be considered.

Preservatives

Most nasal formulations are aqueous based and need preservatives to prevent microbial growth. Parabens, benzalkonium chloride, phenyl ethyl alcohol, EDTA and benzoyl alcohol are some of the commonly used preservatives in nasal formulations. Van De Donk *et. al.*[15] have shown that mercury-containing preservatives have a fast and irreversible effect on ciliary movement and should not be used in nasal systems.

Antioxidants

A small quantity of antioxidants may be required to prevent drug oxidation. Commonly used antioxidants are sodium metabisulfite, sodium bisulfite, butylated hydroxytoluene and tocopherol. Usually, antioxidants do not affect drug absorption or cause nasal irritation. Chemical/physical interaction of antioxidants and preservatives with drugs, excipients, manufacturing equipment and packaging components should be considered as part of the formulation development program.

Humectants

Many allergic and chronic diseases are often connected with crusts and drying of mucous membrane. Certain preservatives/ antioxidants among other excipients are also likely to cause nasal irritation especially when used in higher quantities. Adequate intranasal moisture is essential for preventing dehydration. Therefore, humectants can be added especially in gel-based nasal products. Humectants avoid nasal irritation and are not likely to affect drug absorption. Common examples include glycerin, sorbitol and mannitol.

Role of Absorption Enhancers

When it becomes difficult for a nasal product to achieve its required absorption profile, the use of absorption enhancers is recommended. The selection of absorption enhancers is based upon their acceptability by regulatory agencies and their impact on the physiological functioning of the nose. Absorption enhancers may be required when a drug exhibits poor membrane permeability, large molecular size, lack of lipophilicity and enzymatic degradation by aminopeptidases.

Effect of Pathological Condition

Intranasal pathologies such as allergic rhinitis, infections, or previous nasal surgery may affect the nasal mucociliary transport process and/or capacity for nasal absorption. During the common cold, the efficiency of an intranasal medication is often compromised. Nasal clearance is reduced in insulin-dependent diabetes. Nasal pathology can also alter mucosal pH and thus affect absorption of drugs.

MECHANISM OF DRUG ABSORPTION

Several mechanisms have been proposed but the following two mechanisms have been considered predominantly. The first mechanism involves an aqueous route of transport, which is also known as the paracellular route. This route is slow and passive. There is an inverse log-log correlation between intranasal absorption and the molecular weight of water-soluble compounds. Poor bioavailability was observed for drugs with a molecular weight greater than 1000 Daltons.

The second mechanism involves transport through a lipoidal route that is also known as the transcellular process and is responsible for the transport of lipophilic drugs that show a rate dependency on their lipophilicity. Drugs also cross cell membranes by an active transport route via carrier-mediated means or transport through the opening of tight junctions. For example, Chitosan, a natural biopolymer from shellfish, opens tight junctions between epithelial cells to facilitate drug transport.[6]

FORMULATION DESIGN

Physicochemical Properties of Drugs

Chemical Form: The chemical form of a drug can be important in determining absorption. For example, conversion of the drug into a salt or ester form can alter its absorption. Huang *et. al.*[7] studied the effect of structural modification of drug on absorption. It was observed that in-situ nasal absorption of carboxylic acid esters of L-Tyrosine was significantly greater than that of L-Tyrosine.

Polymorphism: Polymorphism is known to affect the dissolution rate and solubility of drugs and thus their absorption through biological membranes. It is therefore advisable to study the polymorphic stability and purity of drugs for nasal powders and/or suspensions.

Molecular Weight: A linear inverse correlation has been reported between the absorption of drugs and molecular weight up to 300 Daltons. Absorption decreases significantly if the molecular weight is greater than 1000 Daltons except with the use of absorption enhancers.

Particle Size: It has been reported that particle sizes greater than 10 •m are deposited in the nasal cavity. Particles that are 2 to 10 µm can be retained in the lungs,and particles of less than 1 µm are exhaled.

Solubility & Dissolution Rate: Drug solubility and dissolution rates are important factors in determining nasal absorption from powders and suspensions. The particles deposited in the nasal cavity need to be dissolved prior to absorption. If a drug remains as particles or is cleared away, no absorption occurs.

Delivery Systems

The selection of delivery system depends upon the drug being used, proposed indication, patient population and last but not least, marketing preferences. Some of these delivery systems and their important features are summarized below:

Nasal Drops: Nasal drops are one of the most simple and convenient systems developed for nasal delivery. The main disadvantage of this system is the lack of dose precision and therefore nasal drops may not be suitable for prescription products. It has been reported that nasal drops deposit human serum albumin in the nostrils more efficiently than nasal sprays.

Nasal Sprays: Both solution and suspension formulations can be formulated into nasal sprays. Due to the availability of metered dose pumps and actuators, a nasal spray can deliver an exact dose from 25 to 200 µL. The particle size and morphology (for suspensions) of the drug and viscosity of the formulation determine the choice of pump and actuator assembly.

Nasal Gels: Nasal gels are high-viscosity thickened solutions or suspensions. Until the recent development of precise dosing devices, there was not much interest in this system. The advantages of a nasal gel include the reduction of post-nasal drip due to high viscosity, reduction of taste impact due to reduced swallowing, reduction of anterior leakage of the formulation, reduction of irritation by using soothing/emollient excipients and target delivery to mucosa for better absorption. A Vitamin B12 gel has been recently developed as a prescription product.[8]

Nasal Powders: This dosage form may be developed if solution and suspension dosage forms cannot be developed e.g., due to lack of drug stability. The advantages to the nasal powder dosage form are the absence of preservative and superior stability of the formulation. However, the suitability of the powder formulation is dependent on the solubility, particle size, aerodynamic properties and nasal irritancy of the active drug and/or excipients. Local application of drug is another advantage of this system but nasal mucosa irritancy and metered dose delivery are some of the challenges for formulation scientists and device manufacturers.

Generally, the absorption enhancers act via one of the following mechanisms:

- Inhibit enzyme activity;

- Reduce mucus viscosity or elasticity;
- Decrease mucociliary clearance;
- Open tight junctions; and
- Solubilize or stabilize the drug.

Absorption enhancers are generally classified as physical and chemical enhancers. Chemical enhancers act by destructing the nasal mucosa very often in an irreversible way, whereas physical enhancers affect nasal clearance reversibly by forming a gel. The enhancing effect continues until the gel is swallowed. Examples of chemical enhancers are chelating agents, fatty acids, bile acid salts, surfactants, and preservatives. Osmolarity and pH may accelerate the enhancing effect.

TARGET NASAL DRUG DELIVERY

If a nasal formulation is delivered to the target site of absorption (turbinates), benefits can be gained from increased absorption and/or decreased dosage requirements. There may also be a reduction of taste of the drug because of minimum or reduced swallowing of the administered drug. Currently, tip aperture design pumps are available to administer formulations in an upward direction. Because the turbinates are located at the sides of the nostrils (not upward) (Figure 1), the entire dose volume cannot be administered to the target site of absorption. This also leads to swallowing of part of the dose. It may be possible to design a side aperture pump to direct the entire dose volume directly to the absorption site, the turbinates, for more efficient (target) nasal delivery.

SUMMARY

In order to formulate a nasal formulation with desirable performance and commercial attributes, the drug properties, delivery system and nasal physiology should all be considered and understood from the early stages of a product development. It is advisable to focus on maximizing the residence time and ensuring an efficient absorption of drug. A successful nasal formulation program involves detailed consideration of the interactions between formulation composition, device design, delivery system and the patient's pathological condition.

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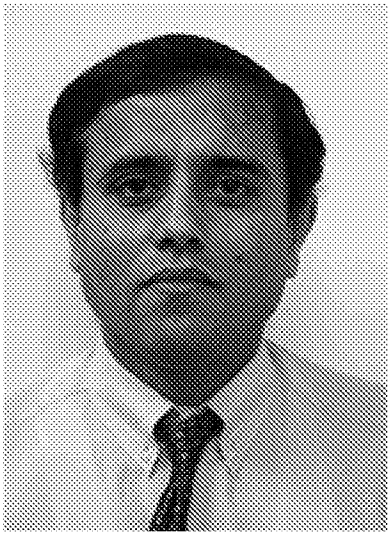
BIOGRAPHY



Dr. Jack Aurora currently serves as Director of Formulation Development at Labopharm, Inc, a specialty pharmaceutical company focused on controlled-release drug delivery and the development of pharmaceutical products incorporating its proprietary technologies. His responsibilities include timely development of formulations in accordance with internally or externally generated product profiles to meet the company's objectives and thereby facilitate efficient decision-making within and outside the group. As a part of the R&D Operations Management Team, he also assists in the efficient identification, development, scale-up and production of formulations chosen for further development. Dr. Aurora is also a consultant with Council of Healthcare Advisors, an association of leading physicians, scientists, and other healthcare professionals. He also teaches courses on Pharmaceutical Product Formulation Development at Seneca College in Toronto. His research focuses include development of Controlled-Release Systems, Pelletization Technology and Nasal Formulation Development. In the field of controlled-release development, he has one US patent to his credit and another four are in process. Prior to joining Labopharm, Dr. Aurora worked at Patheon, Inc, as Manager of Formulation Development, where he was responsible for formulation development and business support activities for various clients involving solids, semi-solids, and nasal (NDA) product development.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: 4912
LULLA *et al.*	Art Unit: 1616
Appl. No. 10/518,016	Examiner: Nielsen, Thor B.
Filed: July 6, 2005	Atty. Docket: PAC/20632 US (4137-04700)
For: **Combination Of Azelastine and Steroids**	

Declaration of Joachim Maus, MD, Under 37 C.F.R. § 1.132

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

Sir:

1. I, Joachim Maus, MD, hereby declare and state as follows:

2. I am currently employed by Meda Pharma GmbH & Co. KG (hereinafter "Meda") as the Director Clinical Development. Meda Pharmaceuticals, Inc. is the licensee of the above-referenced U.S. Application No. 10/518,016 ("the '016 application"). Meda AB is the parent company of Meda Pharma GmbH & Co. KG and Meda Pharmaceuticals, Inc.

3. I hold a doctorate degree in humane medicine from the Johann Wolfgang Goethe University Frankfurt am Main, Germany. A copy of my *Curriculum Vitae* is attached herewith as Exhibit A.

4. As stated in my *Curriculum Vitae*, I have been employed by Meda since its acquisition of VIATRIS in 2005. I have held the position of Director Clinical Development since June 2004 at VIATRIS/ MEDA. I am a specialist in internal medicine and have extensive experience in the respiratory / allergy area. Under my direction, e.g., our inhaled

drugs salbutamol, formoterol and budesonide have been approved for the treatment of asthma and COPD in several European countries, and azelastine eyedrops have been approved for the treatment of allergic conjunctivitis in Australia.

5. As discussed in detail below, at the time of the filing of the '016 application, the clinically significant effect obtained from administering fluticasone propionate and azelastine hydrochloride in an intranasal pharmaceutical composition would not have been predictable.

6. I have read and understand the claims set forth in the Amendment and Reply filed concurrently herewith in the '016 application.

7. A randomized, double-blind, placebo-controlled clinical study was performed in patients with seasonal allergic rhinitis using an intranasal pharmaceutical combination containing fluticasone propionate and azelastine hydrochloride within the scope of the claims of the '016 application. The results of that study are summarized herein.

8. 610 patients were randomized into treatment groups that included a combination therapy nasal spray containing fluticasone propionate and azelastine hydrochloride, versus placebo, a commercially available fluticasone propionate monotherapy, and a commercially available azelastine hydrochloride nasal spray monotherapy, in the Texas Mountain Cedar allergy season. The study compared the combination therapy nasal spray, placebo, azelastine hydrochloride monotherapy nasal spray (Meda Pharmaceuticals Inc.) and fluticasone propionate monotherapy nasal spray (Roxane Labs.), which were each administered as one spray per nostril twice daily (AM and PM). The total daily doses of azelastine hydrochloride and fluticasone hydrochloride were 548 ug and 200 ug, respectively. The primary efficacy variable was change from baseline in the 12-

hour reflective total nasal symptom score (rTNSS), comprising the symptoms of nasal congestion, sneezing, itchy nose, and runny nose. Symptoms were scored twice daily on a 4-point scale (0-3; daily maximum rTNSS=24 points). Current European Medicines Agency guidance recommends adding responder analyses when describing clinical relevance of new therapies. In accordance with this suggestion, this post-hoc analysis considered a reduction of 50% rTNSS as a clinically-relevant response. Kaplan-Meier estimates and pairwise log-rank tests were applied to the ITT subset (n=607) to analyze treatment differences.

9. After 2 weeks of treatment, the combination therapy reduced the mean rTNSS from baseline by a significantly greater extent (-5.31) than either azelastine hydrochloride monotherapy (-3.25; $p<0.001$), fluticasone hydrochloride monotherapy (-3.84; $p=0.003$), or placebo (-2.20; $p<0.001$).

10. A 50% response was achieved by 49.1% of the combination therapy patients, versus 37.4% of the azelastine hydrochloride monotherapy patients, 38.2% of the fluticasone propionate monotherapy patients, and 28.3% of the placebo patients.

11. The response was reached statistically and significantly earlier with the combination therapy ($p=0.0284$ versus fluticasone propionate monotherapy; $p=0.0223$ versus azelastine hydrochloride monotherapy; and $p<0.0001$ versus placebo). A 50% improvement in $\geq$ 30% of the study patients was observed 5-6 days earlier with the combination nasal spray (on day 5), versus fluticasone propionate (on day 11) and azelastine hydrochloride monotherapy (on day 10). This is shown in the Table and in the line graph attached herewith as Exhibit B. In Exhibit B, the fluticasone propionate/azelastine hydrochloride combination therapy is "MP29-02," the azelastine hydrochloride monotherapy is "AZE," the fluticasone propionate monotherapy is "FLU," and the placebo is "PLA."

12. A separate randomized, double-blind, placebo-controlled clinical study was performed in patients with seasonal allergic rhinitis, during the Fall season, using the same intranasal pharmaceutical fluticasone propionate/azelastine hydrochloride combination therapy within the scope of the claims, fluticasone propionate monotherapy and azelastine hydrochloride monotherapy, in order to assess the efficacy of those treatments on ocular symptoms.

13. 779 patients were randomized into treatment groups that included the combination therapy nasal spray containing fluticasone propionate and azelastine hydrochloride, versus placebo, fluticasone propionate monotherapy, and azelastine hydrochloride nasal spray monotherapy. All treatments were administered as 1 spray per nostril twice daily (AM and PM) in the same delivery device and based on the same pharmaceutical formulation. The total daily doses of azelastine hydrochloride and fluticasone propionate were 548 µg and 200 µg, respectively.

14. The primary efficacy variable was change from baseline in 12-hour reflective total nasal symptom score (rTNSS). The main secondary endpoint was the reflective total ocular symptom score (rTOSS), which is a composite score comprising the individual symptoms of eye itching, watery eyes and eye redness. Each symptom was assessed on a 4-point scale (0-3) in the morning and evening, thus leading to a maximum daily rTOSS of 18. Another ocular endpoint assessed was the eye domain of the rhinoconjunctivitis related quality of life questionnaire (RQLQ).

15. Over the entire 2 week treatment period, the fluticasone propionate and azelastine hydrochloride combination therapy reduced the mean rTOSS from baseline to a greater extent (-3.56) than azelastine hydrochloride monotherapy (-2.96; p=0.069), achieving

statistical significance versus fluticasone propionate monotherapy (-2.68; p=0.009) and placebo (-2.02; p<0.001). All individual ocular symptoms contributed to this effect, reaching statistical significance for the individual symptom of watery eyes versus fluticasone propionate monotherapy (p=0.002) and azelastine hydrochloride monotherapy (p=0.026), as well as in eye itching versus fluticasone propionate monotherapy (p=0.004).

16. Furthermore, the combination therapy reduced the RQLQ eye symptoms domain score by a greater margin (-1.72) than azelastine hydrochloride monotherapy (-1.48; p=0.097), and was statistically superior to fluticasone propionate monotherapy (-1.35; p=0.013) and PLA (-0.95; p<0.001) in this regard. Therefore, in addition to nasal symptoms, the combination therapy reduced the total ocular symptom complex which translates into improved quality of life for patients.

17. Taken together, the intranasal combination therapy provided five unexpected benefits: (1) reduced rTNSS, (2) an increase in the number of patients who responded to treatment, (3) a faster response time, (4) improved quality of life, and (5) an improvement in ocular symptoms.

18. A number of studies examined the possibility of achieving additional clinical benefit by combining a nasal steroid with an oral antihistamine in the treatment of allergic rhinitis. *See, e.g.* Juniper *et al.*, *J. Allergy Clin. Immunol. 83(3)*:627-633 (1989), attached herewith as Exhibit C; Ratner *et al.*, *J. Fam. Pract. 47(2)*:118-125 (1998), attached herewith as Exhibit D; and Simpson, R. J., *Ann. Allergy 73(6)*:497-502 (1994), attached herewith as Exhibit E.

19. These studies showed that the combination of an oral antihistamine with a nasal steroid provided either no or minimal additional clinical benefit, with respect to

improvement in rhinitis symptoms, total rhinitis symptom scores, and health-related quality of life measures in patients with allergic rhinitis than the nasal steroid alone. For example, in a study examining the administration of fluticasone propionate and loratadine alone or in combination, no clinical benefit was observed in TNSS (itchy nose, sneezing, runny nose, nasal congestion) or Rhinitis Quality of Life Questionnaire (RQLQ) when comparing the combination of these agents versus fluticasone propionate alone (Ratner *et al.*, Exhibit D).

20. Howarth (*Allergy 62*: 6-11 (2000), copy attached herewith as Exhibit F) likewise reported no clinical evidence to support combining an intranasal corticosteroid with an oral antihistamine for treatment of allergic rhinitis. In fact, these references discourage the use of intranasal corticosteroids with oral antihistamines, due to the absence of clinical benefit and increased cost of combination therapy.

21. Similarly, Nielsen *et al.*, (*Drugs 61*: 1563-1579 (2001), copy attached herewith as Exhibit G) reported at page 1573 that the common clinical practice of combining intranasal corticosteroids with oral antihistamines in the treatment of allergic rhinitis "has no support in clinical evidence, as the combination has not provided effects beyond [the intranasal corticosteroid] alone . . . ." In the abstract Nielson says: "Similarly, comparisons of topical and oral antihistamines have been unable to demonstrate superior efficacy for one method of administration over the other". It further reads: "Combining antihistamines and intranasal corticosteroids in the treatment of allergic rhinitis does not provide any additional effect to intranasal corticosteroids alone."

22. Consequently, the post-filing date review article Salib *et al.* (*Drug Safety 26*: 863-893 (2003), copy attached herewith as Exhibit H) reported at page 886 that "[t]here is no evidence that combining intranasal corticosteroids and intranasal antihistamines provides

any additional therapeutic benefit to intranasal corticosteroids alone" (citing Nielsen *et al.*, Exhibit G and Howarth *et al.*, Exhibit F).

23. In view of the literature discussed above, the superior results obtained for the fluticasone propionate and azelastine hydrochloride combination intranasal formulation ((1) reduced rTNSS, (2) an increase in the number of patients who responded to treatment, (3) a faster response time, (4) improved quality of life, and (5) an improvement in ocular symptoms) would clearly have been unexpected at the time of filing the '016 application.

24. I further state that all statements made on my own knowledge are true and that all statements made on information and belief are believed to be true and further that willful false statements and the like are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the U.S. Code and may jeopardize the validity of the application or any patent issuing thereon.

16 August 2011
Date

Joachim Maus, MD

Exhibit A

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CURRICULUM VITAE

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Place of Birth:	Frankfurt am Main
Marital Status:	married
Nationality:	German
Religion:	catholic

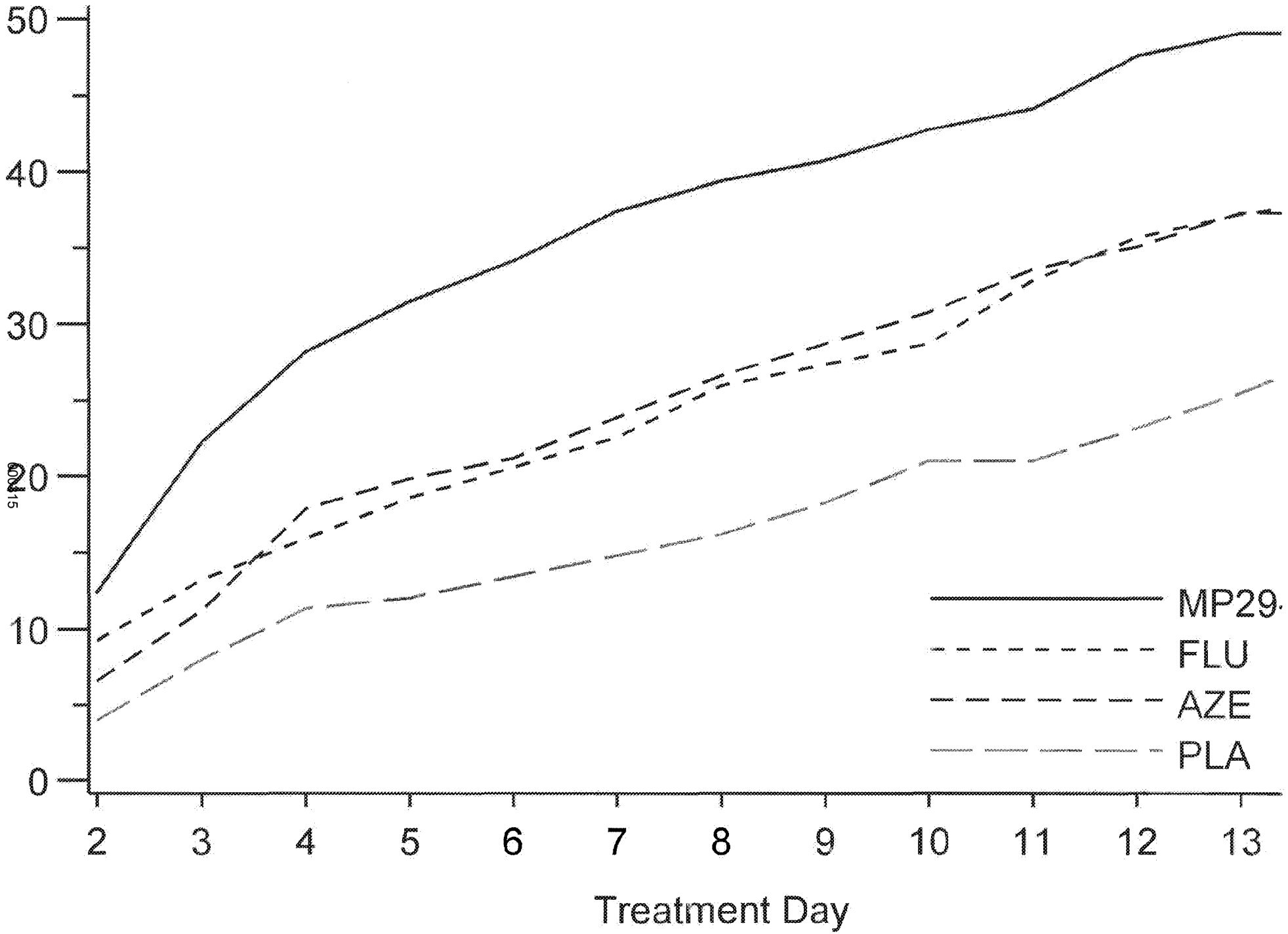
08/77 to 07/86	Leibniz High School of Offenbach / Main
10/86 to 09/91	Medical studies at the Johann Wolfgang Goethe-University of Frankfurt / Main
10/91 to 09/92	Practicum at the Städtische Kliniken Offenbach / Main, Elective course radiology
07.10.92	3rd state board for medical certification
01/93 to 06/94	Practicing license and certification as physician
07/94 to 01/02	Assistant at the department of internal medicine of the Ketteler hospital, Offenbach / Main; Participation in the following trials: HOPE, HOPE TOO, INJECT, GUSTO IIb, HIT-4, MERIT, SPICE, CHARM, MOSES
1995 until 2002	Establishment and responsibility for department of sleep, recognition from German society of sleep medicine (DGSM), extension to 2 beds
22.02.96	Competence for radiation protection in emergency diagnostics
07.10.97	Competence for rescue service
24.04.98	Thesis for doctorate degree „Do the Aggression of Breast Cancer Depend on Age?“ at Johann Wolfgang Goethe-University Frankfurt
22.03.00	Qualification as specialist in internal medicine
since 01.02.02	Medical advisor in the department of clinical pharmacology of ASTA Medica / VIATRIS Frankfurt Main, MEDA Pharma Bad Homburg
since 01.10.02	Promotion to Head of Human Pharmacology – in charge of own phase I unit with 4 physicians, 4 study nurses and assistants
since 02/2003	After restructuring and closing down of human pharmacology Head of Clinical Research and Distribution Manager for trial medication
since 06/2004	Promotion to Director Clinical Development with pan-European responsibility for the three departments Clinical Research(preclinical and clinical studies phase I-IV, IIT, NIS), Biostatistics & Information (safety database, data transfers), and Drug Safety with about 30 academic employees
since 03/2005	Additional responsibility for department Special Projects Neurology

10/08/2011 (Joachim Maus)

TAB 6.1.1.1: Reflective TNSS (AM+PM) / response
Study MP-4001
Response: at least 50 percent change from baseline (ITT)
Responder rates by time

Day	Responder rate [%] MP29-02	AZE	FLU	PLA
2	12.4	6.6	9.3	4.0
3	22.3	11.3	13.2	8.0
4	28.2	17.9	15.9	11.4
5	31.5	19.9	18.6	12.1
6	34.1	21.2	20.6	13.4
7	37.4	23.9	22.6	14.8
8	39.4	26.6	26.0	16.2
9	40.8	28.7	27.4	18.3
10	42.8	30.8	28.7	21.0
11	44.1	33.6	32.9	21.0
12	47.6	35.1	35.7	23.2
13	49.1	37.4	37.2	25.5
14	49.1	37.4	38.2	28.3

Responder rates derived by applying Kaplan-Meier product-limit estimator in PROC LIFETEST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30
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10
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2
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6
7
8
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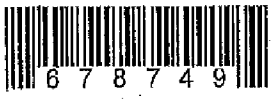
11
12
13
Treatment Day
MP29
FLU
AZE
PLA

Exhibit C

WISCONSIN Information Retrieval For Business and Industry
TECH SEARCH

WTS Number: 678749



Request Date: 2/11/11 2:42 PM
Conf Number: 214295
Requester: Timothy Jones
Sterne Kessler Goldstein & Fox
1100 New York Avenue, NW, Suite 900
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Requester Email: Tjones@skgf.com
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Reference: 2286.0030002

Delivery: Email
Instructions:

1)Juniper et al., J. Allergy Clin. Immunol. 83(3):627-633 (1989);

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Comparison of beclomethasone dipropionate aqueous nasal spray, astemizole, and the combination in the prophylactic treatment of ragweed pollen–induced rhinoconjunctivitis

E. F. Juniper, MSc, P. A. Kline, RN, F. E. Hargreave, MD, and J. Dolovich, MD
Hamilton, Ontario, Canada

The clinical efficacy and side effect of (1) beclomethasone dipropionate aqueous nasal spray, 400 μg daily, (2) astemizole, 10 mg daily, and (3) beclomethasone, 400 μg, plus astemizole, 10 mg daily, were compared in a double-blind, randomized, parallel-group trial. Ninety adults were matched into groups of three according to sensitivity to ragweed pollen. One of each of the three subjects was assigned to nasal spray alone, one was assigned to astemizole alone, and one subject was assigned to both medications. Medications were started 1 week before and continued daily until 1 week after the ragweed-pollen season (6 weeks). If rhinoconjunctivitis was inadequately controlled with the trial medications, pressurized steroid nasal spray and/or antihistamine-decongestant eye drops were used in the minimum dose that would ensure relief. Nose and eye symptoms and concomitant medication use were recorded daily in a diary. Sneezing, nasal obstruction, and rhinorrhea were significantly better, and less additional nasal spray was used in subjects taking beclomethasone alone than in subjects taking astemizole alone. Beclomethasone plus astemizole provided no better control of rhinitis than beclomethasone alone. Eye symptoms and eye drop use tended to be less in subjects taking astemizole alone than in subjects taking beclomethasone alone, but the best control of eye symptoms was recorded in the subjects taking both trial medications. Side effects were mild or transient. (J ALLERGY CLIN IMMUNOL 1989;83:627-33.)

Antihistamine tablets and intranasal steroid spray have been used successfully to treat rhinoconjunctivitis induced by seasonal pollens.[1, 2] Most previous comparisons have suggested that nasal symptoms may be controlled better by steroid nasal sprays,[3-6] although the conclusions are not unanimous,[7] and that conjunctivitis is treated more effectively by antihistamines.[4-7] These results and the different pharmacologic properties of the two types of treatment suggest that a combination of nasal steroid and antihistamine may be the most effective approach of overall treatment.

In the last few years, effective, nonsedative antihistamines have become popular for the treatment of seasonal allergic rhinoconjunctivitis. More recently, aqueous steroid nasal sprays, with efficacy comparable to the original Freon-propelled delivery system, but with less nasal bleeding and drying, have been introduced.[8] The pharmacologic profile of nasal steroids suggests that the most effective approach to treatment is regular prophylactic use[9]; therefore, an aqueous delivery system should be effective in achieving this with a reduced risk of side effects. In this study, we have compared the clinical efficacy of beclomethasone dipropionate aqueous nasal spray (Aq. Beconase; Glaxo Canada, Inc., Toronto, Ontario, Canada), taken before and continued daily throughout the ragweed-pollen season, with that of astemizole (Hismanal; Janssen Pharmaceutica, Inc., Mississauga, Ontario, Canada), a nonsedative antihistamine whose pharmacologic profile also recommends prophylactic and continuous treatment for allergic rhinoconjunctivitis.[10] We have also examined whether taking the two medications together produces better symptom control than taking either medication individually.

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Reprint requests: E. F. Juniper, MSc, Department of Clinical Epidemiology and Biostatistics, McMaster University Medical Center, 1206 Main St., West, Hamilton, Ontario, Canada L8N 325.

TABLE I. Subject characteristics

	Astemizole alone	Beclomethasone alone	Beclomethasone plus astemizole
No.	30	30	30
Sex (M/F)	16/14	15/15	15/15
Age (mean, SD)	39.8 (13.5)	41.3 (11.8)	42.2 (13.8)
Initial ragweed skin sensitivity (mean wheal diameter)			
<2.5 mm	3	3	3
2.5-3.0 mm	4	4	4
3.0-3.5 mm	8	6	7
3.5-4.0 mm	5	7	6
4.0-4.5 mm	6	5	6
>4.5 mm	4	5	4
Severity of ragweed rhinoconjunctivitis the previous year			
1*	5	5	6
2†	5	5	7
3‡	16	12	11
4§	1	6	5
5‖	3	2	1
History of asthma	5	7	6
Sensitivity to fungal spores	5	4	5
Sensitivity to grass pollen	18	15	20

*Symptoms were well controlled with antihistamine or nasal spray.
†Symptoms were well controlled with antihistamine plus nasal spray or mild symptoms when subject was treated with antihistamine or nasal spray.
‡Mild symptoms when subject was treated with antihistamine plus nasal spray or moderate symptoms when subject treated with antihistamine or nasal spray.
§Moderate symptoms when subject was treated with antihistamine plus nasal spray or severe symptoms when subject was treated with antihistamine or nasal spray.
‖Severe symptoms when subject was treated with antihistamine plus nasal spray.

MATERIAL AND METHODS

Subjects

Ninety ragweed pollen–sensitive adults, aged 18 to 70 years, who were either attending the Firestone Regional Chest and Allergy Clinic or who responded to a newspaper article, participated in the study. All subjects gave a history of rhinoconjunctivitis that required treatment during the previous two ragweed-pollen seasons, and all subjects had a positive response to skin prick test with ragweed-pollen extract. None of the subjects had perennial rhinitis, and none were more than mildly sensitive to the fungal spores that are in the air at the same time as ragweed pollen. None of the subjects had serious illness other than seasonal rhinitis or asthma. Pregnant and nursing mothers were excluded, and women of childbearing potential were advised to use an effective method of birth control throughout the study and for 2 months thereafter. None of the subjects had taken astemizole, steroid nasal spray, or oral steroid within 6 weeks of enrollment. All subjects signed an informed consent, which, with the study protocol, had been approved by the St. Joseph's Hospital Research Committee.

Study design

The study was designed as a double-blind, randomized, parallel-group comparison of (1) beclomethasone dipropionate aqueous nasal spray, 50 μg per nostril four times daily, (2) astemizole, 10 mg once daily, and (3) beclomethasone dipropionate aqueous nasal spray, 50 μg per nostril four times daily plus astemizole, 10 mg daily. A double-dummy technique was used to achieve blinding.

Three weeks before the anticipated start of the ragweed-pollen season, subjects had duplicate skin prick tests with tenfold serial dilutions of ragweed-pollen extract (25 to 25,000 Noon units, Bencard Allergy Service, Weston, Ontario), with single dilutions of *Alternaria tenuis* and *Cladosporium (Hormodendrum)* (Hollister Steir Laboratories of Canada, Rexdale, Ontario), and mixed grass-pollen extract (Bencard Allergy Service). An allergy history was obtained by questionnaire. Severity of rhinoconjunctivitis during the previous ragweed season was estimated from symptoms and medication requirements (Table I). Subjects were matched into groups of three according to skin sensitivity to the ragweed extract, the severity of ragweed

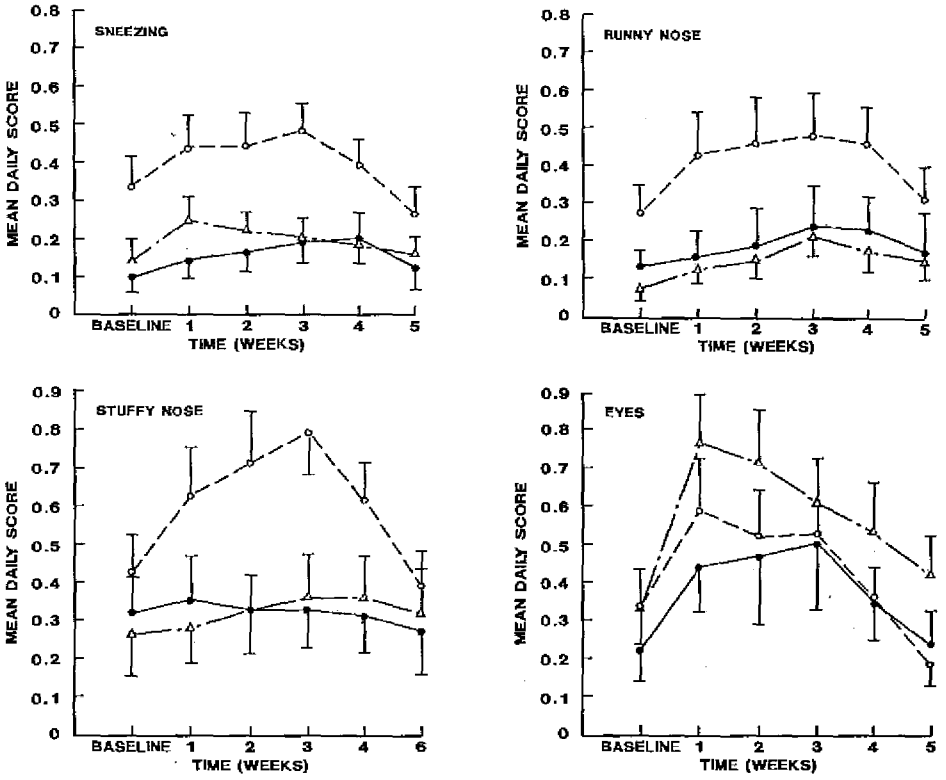

FIG. 1. Mean daily nose and eye symptom scores (SEM) before and throughout the ragweed-pollen season; astemizole alone (○); aqueous beclomethasone nasal spray alone (△); astemizole plus aqueous beclomethasone nasal spray (●).

pollen–induced rhinoconjunctivitis, sensitivity to *Alternaria* and *Cladosporium (Hormodendrum)*, history of asthma, grass-pollen sensitivity, and gender. One of each of the three subjects was assigned randomly to beclomethasone alone, one was assigned to astemizole alone, and one subject was assigned to the combination of beclomethasone and astemizole.

Subjects started taking the trial medication 1 week before ragweed pollen was expected in the air (Monday, August 10) and continued daily until 1 week after the pollen season (Monday, September 21), that is, for a total of 6 weeks. Subjects were instructed to take the tablet in the morning either 1 hour before or 2 hours after food and to use the nasal spray four times per day. If they had difficulty remembering to use the spray at regular intervals, they were allowed to take two doses in the morning and two in the evening. If, during the season, symptoms were not adequately controlled by the trial medications, subjects were instructed to take additional medications in the minimum dose that would keep them well controlled. For nasal symptoms they used Freon-propelled beclomethasone dipropionate nasal spray, one puff (50 μg) into each nostril, when it was needed, up to four times a day. Even for subjects taking the trial beclomethasone, this additional dose provided a total daily amount that was lower than the recommended maximum dose. For eye symptoms, subjects used naphazoline HCl and anatazoline ophthalmic drops, one drop into each eye, when it was needed, up to four times per day. If this treatment was insufficient, sodium cromoglycate eye drops, up to four times per day, were added. Subjects were instructed not to use other medication for rhinoconjunctivitis. Nasal spray and eye drops were selected over an antihistamine tablet as the concomitant medication so that nose and eye symptoms could be evaluated separately. Subjects with asthma used salbutamol aerosol, 200 μg, when it was needed, up to four times per day and those with more severe asthma took beclomethasone dipropionate, 100 μg, up to four times per day. No oral steroids were used. The provision and use of standardized concomitant medications allowed the efficacy of the trial medications to be estimated from the amount of additional medication used, prevented subjects dropping out of the study because of inadequate symptom control, and reduced the risk of subjects using unauthorized hay fever medications.

Subjects made entries in a diary each morning and each evening throughout the study.[11] They recorded the severity (0, absent; 1, mild; 2, moderate; and 3, severe) and duration (0, absent; 1, a few short episodes; 2, many episodes; and 3, continuous) of sneezing, stuffy nose, runny nose, eye symptoms, and asthma. At the end of each day, they recorded the amount of concomitant medication needed in the previous 24 hours.

Subjects attended the clinic after 1, 3, and 6 weeks of treatment. At each visit, symptoms were reviewed to ensure

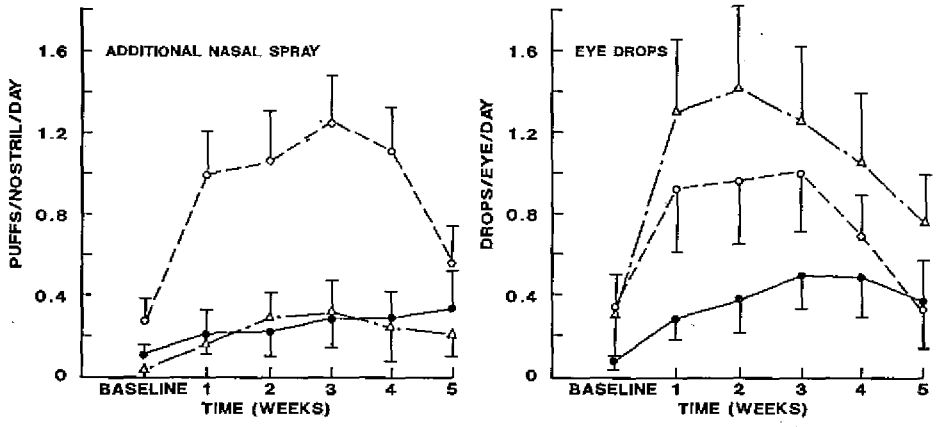

FIG. 2. Mean daily additional medication use (SEM) before and throughout the ragweed-pollen season; astemizole alone (○); aqueous beclomethasone nasal spray alone (△); astemizole plus aqueous beclomethasone nasal spray (●).

TABLE II. Efficacy results (mean daily score)

	Astemizole alone	Beclomethasone alone	Beclomethasone plus astemizole
Overall (mean of 6 weeks)			
Sneezing	0.395	0.193	0.155
Stuffy nose	0.594	0.319	0.322
Runny nose	0.406	0.152	0.192
Eye symptoms	0.424	0.563	0.355
Asthma	0.030	0.015	0.048
Beclomethasone use	0.871	0.206	0.241
Eye drop use	0.707	1.016	0.354
Asthama aerosol use	0.195	0.049	0.113

that they were adequately controlled and diaries were examined for accuracy and completeness. Subjects reported all nonrhinoconjunctivitis symptoms that they had experienced since the previous visit, irrespective of whether they perceived them as trial-medication related. The nasal spray bottles were weighed and tablets were counted for compliance. At all visits except the last, each subject gave a demonstration of the technique of nasal spray application to confirm correct use.

Regular daily ragweed-pollen counts were not available throughout this study. However, intermittent counts were made with a Hirst volumetric spore trap (Burkard Manufacturing Co., Ltd., Richmansworth, Hertfordshire, England). These counts suggested that the duration and severity of the local ragweed-pollen season of the year 1987 was very similar to duration and severity of each of the previous 10 years when regular daily counts were made.[11, 12]

Analysis

Mean daily symptoms and medication scores were calculated for each subject for each of the 6 weeks of the study. These data were analyzed for treatment effect with a repeated measures analysis of variance. Differences between the three treatments were examined with Student's-Newman-Keuls method for multiple comparisons.[13] These data demonstrated instability of variance across the time periods, and therefore, a square root transformation was used to improve their statistical properties. Percent compliance was estimated from the observed and expected bottle-weight loss and tablet use. Differences were considered significant at $p < 0.05$ (two-tailed).

RESULTS

Ninety subjects were enrolled, and eighty-nine completed the study. One subject withdrew because he could not remember to take the trial medication. Demographic and allergy characteristics were well balanced across the three treatment groups (Table I).

In all three treatment groups, nose and eye symptoms were well controlled, as indicated by the highest mean weekly score for any symptom <0.8 (maximum, 3.0) (Figs. 1 and 2). Nevertheless, aqueous beclomethasone was more effective in controlling

TABLE III. Statistical comparison of trial medications (with Student's-Newman-Keuls method for multiple comparisons)

	Astemizole vs beclomethasone	Astemizole vs astemizole plus beclomethasone	Beclomethasone vs astemizole plus beclomethasone
Symptoms			
Sneezing	$p < 0.05$*	$p < 0.05$†	NS
Stuffy nose	$p < 0.05$*	$p < 0.05$†	NS
Runny nose	$p < 0.05$*	$p < 0.05$†	NS
Eye symptoms	NS	NS	NS
Asthma	NS	NS	NS
Concomitant medication use			
Nasal spray	$p < 0.05$*	$p < 0.05$†	NS
Eye drops	NS	NS	NS
Asthma aerosols	NS	NS	NS

NS, Not significant.
*Beclomethasone alone was better than astemizole alone.
†Astemizole plus beclomethasone was better than astemizole alone.

TABLE IV. Compliance (% observed/expected)

	Astemizole alone	Beclomethasone alone	Beclomethasone plus astemizole
Pills (mean, SD)	99.3 (2.8)	100.2 (4.1)	99.2 (4.7)
Nasal spray (mean, SD)	91.8 (14.0)	94.1 (7.6)	91.3 (12.6)

sneezing, stuffy nose, and runny nose than astemizole ($p < 0.05$), as demonstrated both by lower symptom scores and less need for additional nasal spray (Figs. 1 and 2; Tables II and III). For nasal symptoms, the subjects who took both aqueous beclomethasone and astemizole were better protected than subjects taking astemizole alone but no different from subjects taking nasal spray alone. For each of the 6 weeks of the study, sneezing, stuffy nose, and runny nose demonstrated similar treatment differences, suggesting the treatments had similar time courses on each of these symptoms (Fig. 1). As might have been expected, subjects taking astemizole alone had lower eye symptom scores than subjects taking beclomethasone alone, but the lowest eye scores and the least need for additional eye drops was demonstrated by the subjects taking both astemizole and beclomethasone. However, these differences for eye symptoms and eye drops did not reach statistical significance, possibly as a result of poor statistical power, since not all subjects gave a history of allergic conjunctivitis. Asthma symptoms and medication requirements were similar in the three groups.

Compliance with taking the trial medications was very good (Table IV) with no differences between the three treatment groups. The most common side effect was drowsiness, which was reported on one or more occasions by nine subjects taking astemizole alone, four subjects taking beclomethasone alone, and four subjects taking the combined medications (Table V). In most cases the drowsiness was mild and transient. However, it was troublesome in one subject taking astemizole alone, but he elected to continue taking the medication because his rhinoconjunctivitis was well controlled. The subjects who reported drowsiness experienced a wide range of rhinoconjunctivitis severity; therefore, it was not possible to evaluate whether the drowsiness was caused by persistent symptoms, the trial medications, the direct effect of the ragweed,[14] or factors unrelated to the study. Although some subjects reported hunger during the study, none experienced inappropriate weight gain.

DISCUSSION

The results of this study have demonstrated that seasonal allergic rhinitis is more effectively controlled by the regular use of beclomethasone dipropionate aqueous nasal spray (400 μg daily) than by the regular use of astemizole (10 mg daily). Results have also demonstrated that there is no further improvement in

TABLE V. Number of subjects reporting adverse experiences

Adverse experience	Astemizole alone	Beclomethasone alone	Beclomethasone plus astemizole
Drowsiness	9	4	4
Hunger	3	3	4
Dry nose/lips/mouth/throat	3	2	2
Nasal bleeding	0	2	3
Headache	1	1	3
Thirst	0	2	1
Skin irritation/rash	0	2	1
Nausea	0	0	2

nasal symptoms when astemizole is added to the beclomethasone. For eye symptoms, astemizole alone tended to be more effective than beclomethasone alone, but the addition of beclomethasone to the astemizole provided even lower eye scores.

The prophylactic and continuous use of steroid nasal sprays has been limited in the past by nasal dryness and bleeding, apparently induced by the Freon-propelled aerosol delivery system.[9] However, the aqueous delivery system appears to have reduced the side effects without loss of efficacy,[8] thus permitting optimal use of this medication. In the present study, care was taken to instruct subjects in the correct use of the aqueous nasal spray because the technique of application appears to be a little more subject to error than the Freon-pressurized delivery system. Each subject's technique was checked regularly, and the spray bottles were weighed to ensure that maximum efficacy was being achieved.

Comparisons between the the new nonsedative antihistamines have demonstrated that astemizole is one of the most effective in controlling symptoms of seasonal allergic rhinoconjunctivitis.[12, 15, 16] It has a slow onset of action, not reaching steady-state serum levels for 1 to 2 weeks.[10] Therefore, it would be expected to achieve maximum therapeutic effect when it was used in a schedule similar to that for steroid nasal spray, namely, started before and continued daily throughout the pollen season.

Previous comparisons of antihistamines and steroid nasal sprays have suggested that nasal symptoms are controlled more effectively by nasal sprays, but the results are not unanimous. Two studies have suggested that the nasal sprays are more effective for controlling nasal blockage but similar to antihistamines for sneezing and rhinorrhea.[3, 4] One study suggested that sneezing and rhinorrhea are controlled better by steroid nasal spray but similar for nasal blockage.[6] Another study suggested that all nasal symptoms, except sneezing, are better with nasal spray treatment.[5] One study concluded that nasal spray and antihistamines are of similar effectiveness for all nasal symptoms.[7] Differences in conclusions may have occurred as a result of variation in the types of trial medications and differences in dosing schedules. In this study, when both trial medications were used in a manner that would appear optimal for their pharmacologic properties, the aqueous beclomethasone nasal spray was significantly more effective than astemizole for all three nasal symptoms monitored. The results also demonstrated that subjects who used both astemizole and beclomethasone had less nasal symptoms than subjects receiving astemizole alone. This conclusion is in agreement with Wihl et al.[17] who demonstrated that, even after subjects had demonstrated symptomatic improvement with astemizole, further improvement could be achieved by adding beclomethasone dipropionate nasal spray. The results of the present study add the further observation that beclomethasone nasal spray alone is just as effective as beclomethasone plus astemizole for nasal symptoms, suggesting that nasal spray alone may be sufficient for the optimal treatment of symptoms.

Astemizole was more effective than the aqueous nasal spray at controlling eye symptoms. However, it was interesting to observe that the best control of eye symptoms was achieved by the subjects taking the two medications together. The same observation has been made with another aqueous steroid nasal spray, budesonide,[4] but the mechanism by which this may occur is unclear. It may be that, by keeping the nasal passages clear, nasolacrimal duct drainage and eyelid venous congestion are improved. It could be that some nasal spray reaches the eye through the nasolacrimal duct, but this appears unlikely, and, at present, there is no evidence to support this hypothesis. It may also be that, if nasal symptoms are minimal, psychologically the patient is not so troubled by eye symptoms

and records lower scores. However, these are only speculations, and further studies will be required to confirm the finding and determine the mechanism.

We thank all the subjects for their diligent participation in the study, Professor Robin Roberts for statistical advice, and Mrs. Laurie Whitely for assisting in the preparation of the manuscript. We thank Iolab Pharmaceuticals for supplying Vasocon-A eye drops and Fisons Pharmaceuticals for Opticrom eye drops.

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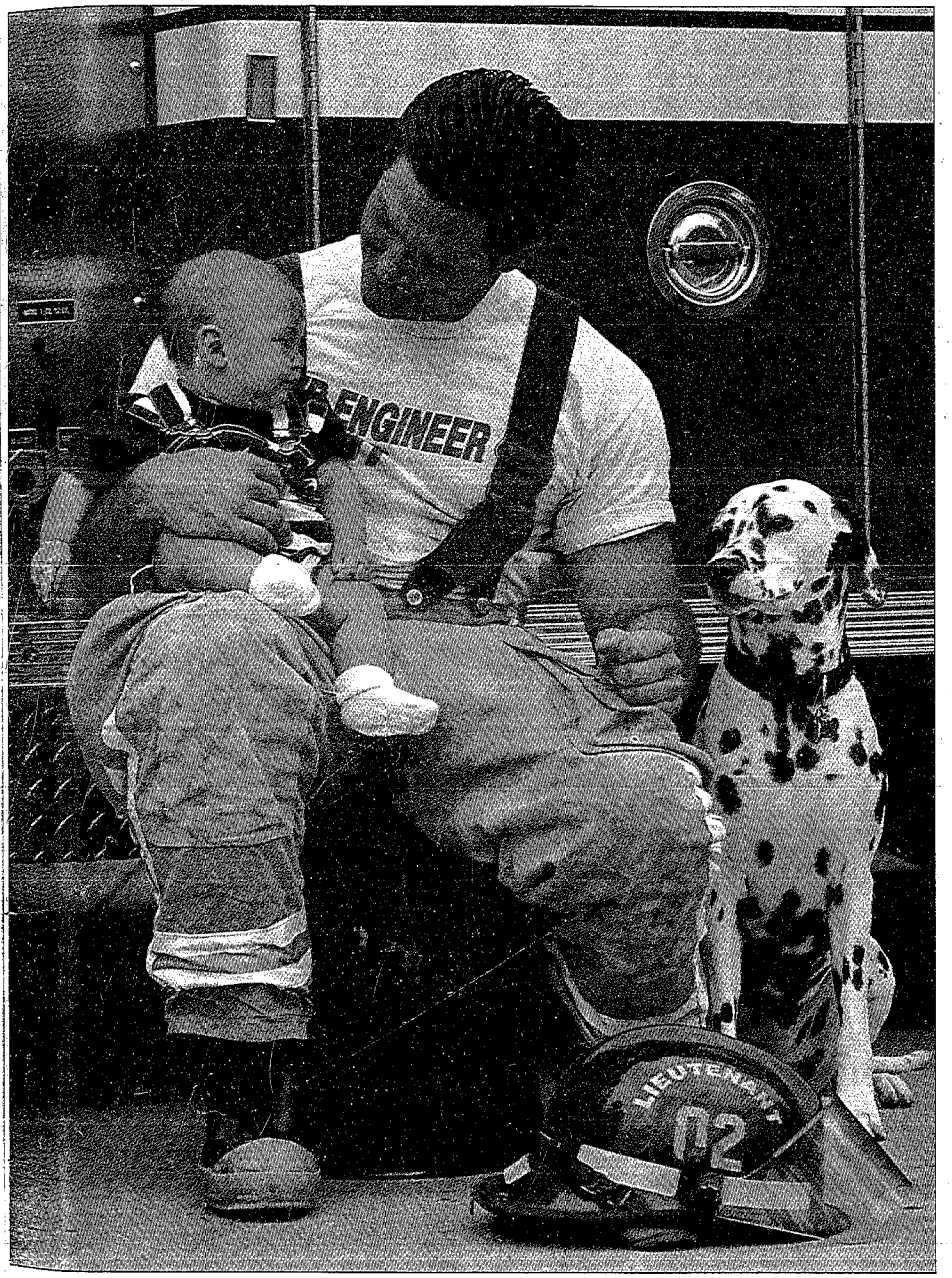

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A Comparison of the Efficacy of Fluticasone Propionate Aqueous Nasal Spray and Loratadine, Alone and in Combination, for the Treatment of Seasonal Allergic Rhinitis

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BACKGROUND. Intranasal corticosteroids and oral antihistamines are both effective in the treatment of seasonal allergic rhinitis, although the therapeutic value of administering the two types of agents concurrently has rarely been evaluated. This study was designed to compare the efficacy, safety, and impact on quality of life of fluticasone propionate aqueous nasal spray (FP ANS), loratadine, FP ANS plus loratadine, and placebo (an aqueous nasal spray plus tablet) in the treatment of seasonal allergic rhinitis during the mountain cedar allergy season in south central Texas.

METHODS. Six hundred patients with seasonal allergic rhinitis were treated for 2 weeks with either FP ANS 200 µg once daily, loratadine 10 mg once daily, the FP ANS and loratadine regimens combined, or placebo in a multicenter, randomized, double-blind, double-dummy, parallel-group study.

RESULTS. Clinician- and patient-rated total and individual nasal symptom scores after 7 and 14 days of therapy and overall evaluations were significantly lower ($P < .001$) in the FP ANS and FP ANS plus loratadine groups compared with the loratadine only and placebo groups. Loratadine was not statistically different from placebo in clinician and patient symptom score ratings nor in overall clinician and patient evaluations. FP ANS plus loratadine and FP ANS monotherapy were comparable in efficacy in almost all evaluations; for some patient-rated symptoms the combination was found superior. Mean score changes in the Rhinoconjunctivitis Quality of Life Questionnaire from baseline to day 14 showed significantly greater improvement ($P < .001$) in quality of life in the FP ANS group than in the group of patients receiving loratadine only or placebo, and no significant benefit was demonstrated in the FP ANS plus loratadine group over the FP ANS monotherapy group. No serious or unusual drug-related adverse events were reported. Combining loratadine with FP ANS did not alter the adverse events profile or frequency.

CONCLUSIONS. In the treatment of seasonal allergic rhinitis, FP ANS is superior to loratadine and placebo, and adding loratadine to FP ANS does not confer meaningful additional benefit.

KEY WORDS. Rhinitis, allergic, seasonal; loratadine; antihistamine; fluticasone propionate aqueous nasal spray [non-MeSH]. *(J Fam Pract 1998; 47:118-125)*

Intranasally administered corticosteroids and nonsedating, second-generation oral antihistamines currently form the core of pharmacotherapy for seasonal allergic rhinitis.[1,2] Both treatments have been shown to alleviate or significantly reduce the rhinorrhea, sneezing, and nasal itching characteristics of allergic rhinitis.[2] While intranasal corticosteroids reduce nasal blockage more effectively than oral antihistamines,[1] antihistamines tend to have a more pronounced effect on eye symptoms.[1,3] The choice of one mode of pharmacotherapy over the other is generally based on patient preference, with the goal of achieving the most effective control of rhinitis symptoms with the fewest side effects.

One currently available intranasal corticosteroid preparation, fluticasone propionate aqueous nasal spray (FP ANS) (Flonase Nasal Spray, 0.05% w/w, Glaxo Wellcome Inc, NC), was developed to provide a high ratio of local anti-inflammatory to systemic activity.[4-7] In clinical trials of 2 to 4 weeks' duration comparing FP ANS with oral antihistamines, FP ANS demonstrated significantly greater effectiveness than loratadine,[8-11] terfenadine,[12-14] astemizole,[15] and cetirizine[16] in relieving nasal symptoms of rhinitis.

Drouin and colleagues[17] have suggested that the concomitant administration of an intranasal corticosteroid regimen with an oral antihistamine regimen

Submitted, revised, May 7, 1998. From Sylvana Research, San Antonio, Texas (P.H.R.); Allergy Associates of Austin Diagnostic Clinic (J.H.V.) and HealthQuest Research (W.C.H), Austin, Texas; Southwest Allergy and Asthma Research Center, San Antonio, Texas (B.G.M.); and Central Texas Health Research, New Braunfels (F.C.H.); Glaxo Wellcome Inc, Research Triangle Park, North Carolina (R.E.W., B.W.B., P.R.R., C.K.C.). *Requests for reprints should be addressed to Paul H. Ratner, MD, Sylvana Research, 7711 Louis Pasteur Drive, Suite 406, San Antonio, TX 78229.*

theoretically should result in greater relief of both nasal and ocular rhinitis symptoms than is achievable with either regimen alone. Although several clinical trials have evaluated the efficacy of intranasal beclomethasone dipropionate in combination with an oral antihistamine,[17-19] and one study has investigated an FP ANS–cetirizine combination,[20] there have been no studies to date evaluating a combination of FP ANS and loratadine. The purpose of the present study was to compare the efficacy, safety, and impact on quality of life of FP ANS, loratadine, FP ANS combined with loratadine, and placebo over a 2-week period in the treatment of nasal symptoms of seasonal allergic rhinitis due to mountain cedar pollen.

METHODS

PATIENTS

Male and nonpregnant female outpatients, aged 12 years or older, were eligible for the study if they had moderate to severe seasonal allergic rhinitis diagnosed according to four criteria: (1) positive (a 2+ reaction, scored on a scale of 0 to 4, defined as a wheal diameter at least 3 mm greater than diluent control) skin test reaction to mountain cedar (*Juniperus ashei*) allergen within 12 months; (2) appearance of the nasal mucosa consistent with a diagnosis of seasonal allergic rhinitis; (3) a history of seasonal onset and offset of symptoms for at least two previous mountain cedar pollen seasons; and (4) moderate to severe symptoms of rhinitis evidenced by patient diary card ratings during a run-in. Patients were ineligible for the study if they had received, before the screening visit, treatment with loratadine within 1 week, astemizole within 6 weeks, cromolyn sodium within 2 weeks, over-the-counter or prescription medications that could affect rhinitis symptomatology (eg, nasal decongestants) within 72 hours, or inhaled, intranasal, or systemic corticosteroids within 1 month. Patients could not have either a septal deviation (>50% blockage) or a nasal polyp that could obstruct penetration of an intranasal spray. Patients were not included if they had a history of nasal septal surgery or nasal septal perforation. Patients were excluded if they had clinically significant physical examination findings at screening, had evidence of candidal infection, or were pregnant or lactating. Patients were also excluded if they had any condition or impairment that might affect their ability to complete the study or provide informed consent.

STUDY DESIGN

The protocol for this double-blind, placebo-controlled, parallel-group comparative trial was approved by an institutional review board for each of the five study sites. All patients or their guardians gave written informed consent. This study was a double-dummy design in which patients randomized to active oral medication received both a placebo nasal spray and active oral medication, and patients randomized to active nasal spray received both the active nasal spray and placebo oral medication. At the screening visit, clinicians evaluated potential study candidates by rating their nasal symptoms (sneezing, nasal blockage, rhinorrhea, and nasal itching) according to a visual analog scale, ranging from 0 (absent) to 100 (severe),[21] and by completing the following: a medical history, skin testing for allergy to mountain cedar allergen (if not done within previous 12 months), a physical examination, clinical laboratory tests, pregnancy test, and an examination of the nose and oropharynx for evidence of *Candida*. Patients who had symptoms began the 7- to 30-day run-in period immediately after screening, and patients who were free of symptoms were instructed to record their allergy symptoms associated with mountain cedar as soon as they began, so that the run-in period could be initiated.

During the run-in period and throughout the study, patients used the visual analog scale described above to rate their nasal symptoms daily on diary cards. Symptoms were rated in the evening to represent symptoms for the entire day. To qualify for enrollment, the total nasal symptom score (derived by adding individual symptom scores for nasal blockage, rhinorrhea, sneezing, and nasal itching for the day) was required to be at least 200 of a possible 400 on 4 of the 7 days immediately preceding enrollment.

Patients who met this criterion were randomly assigned on day 0 (baseline) to receive one of four regimens for 14 days: FP ANS 200 µg (two 50-µg sprays per nostril) plus one placebo capsule (to match the loratadine dosing form) once daily at 8 AM; placebo nasal spray (two sprays per nostril) plus one encapsulated loratadine 10-mg tablet once daily at 8 AM; FP ANS 200 µg (two 50-µg sprays per nostril) plus one encapsulated loratadine 10-mg tablet once daily at 8 AM; placebo spray (two sprays per nostril) plus one placebo capsule once daily at 8 AM. The formulation of loratadine used for encapsulation was Claritin tablets (Schering Corporation, Kenilworth, NJ). Dissolution testing confirmed that active capsules were comparable with unencapsulated tablets.

EFFICACY ANALYSIS

Patients recorded their nasal symptoms and use of study medication daily on diary cards throughout the treatment phase. Nasal symptoms were assessed by the clinician on day 0 (before the first dose of drug was administered), day 7, and day 14. During the treatment period, patients were not permitted to use any other medication that might affect rhinitis symptoms. At every clinic visit, clinicians recorded the occurrence of adverse events (defined as any untoward medical occurrence, drug-related or not), recorded concomitant medications used, checked compliance by diary

card and capsule counts, and examined patients for evidence of nasal and oropharyngeal *Candida*. On day 14, clinicians and patients independently recorded their overall evaluation of treatment, and patients underwent a final physical examination.

Quality-of-Life Analysis

At baseline and on day 14, patients completed the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ).[22] This 28-item, self-administered, disease-specific questionnaire measures quality of life globally and across seven different domains known to be affected by rhinoconjunctivitis: nasal symptoms; eye symptoms; activities; practical problems; sleep; emotional issues; and symptoms other than those involving the nose or eye, such as fatigue, irritability, and tiredness. Patients were asked to rate each item on a 7-point scale (where 0 = not troubled or none of the time and 6 = extremely troubled or all of the time), capturing the impact of rhinoconjunctivitis for each item over the previous 7 days. Each domain provides a scale score, and the mean of all the items provides an overall global score. An improvement in rhinoconjunctivitis quality of life was indicated by a decrease in domain and global scores at day 14.

TABLE 1

Demographic Characteristics and Disposition of Patients

	Placebo	Loratadine*	FP ANS*	FP ANS + Loratadine*
Number of patients	150	150	150	150
Mean age, yr	42.0	40.1	40.7	42.2
Range	16-74	15-70	13-80	15-78
Sex, no. (%)				
Male	61 (41)	69 (46)	68 (45)	74 (49)
Female	89 (59)	81 (54)	82 (55)	76 (51)
Ethnic origin, no. (%)				
White	115 (77)	110 (73)	117 (78)	120 (80)
Hispanic	30 (20)	28 (19)	22 (15)	26 (17)
Other	5 (3)	12 (8)	11 (7)	4 (3)
Compliance† (%)				
With capsule	97.5	97.0	97.8	98.0
With spray	97.9	96.8	97.9	98.2
Patients withdrawn, no. (%)	10 (7)	8 (5)	8 (5)	5 (3)
Adverse event	3 (2)	2 (1)	3 (2)	0 (0)
Failed to return	2 (1)	0 (0)	0 (0)	1 (<1)
Lack of efficacy	4 (3)	3 (2)	4 (3)	2 (1)
Other	1 (1)	3 (2)	1 (<1)	2 (1)

* FP ANS = fluticasone propionate aqueous nasal spray 200 µg daily; loratadine dosage is 10 mg once daily.
† Percent of patients who took at least 80% of study medication.

Statistical Analysis

All patients randomly assigned to treatment received at least one dose of the study drug, and reported baseline scores were included in the analysis. Patients remained in the analysis (daily and weekly timepoints) until their efficacy scores were missing because of withdrawal or loss to follow-up. All tests performed tested two-sided hypotheses, and a difference was considered statistically significant when the two-tailed P value was ≤.05. Efficacy measures were changes in mean clinician- and patient-rated nasal symptoms (both total and individual nasal symptom scores), and frequency of patient- and clinician-scored ratings of overall response to treatment. It was estimated that 150 patients per treatment arm would provide approximately 80% power to detect a difference between active treatments of at least 30 in mean change from baseline in clinician-rated and patient-rated total nasal symptom scores at a significance level of .05. Demographic and baseline disease characteristics of patients were summarized by treatment group. The chi-square test was performed to compare differences with respect to sex, ethnic origin, childbearing potential, pregnancy status, type of birth control used, and clinician- and patient-rated overall evaluations. The analysis of variance F test was used to compare differences with respect to age, sex, ethnic origin, and individual and total clinician- and patient-rated symptom scores. In the RQLQ, descriptive statistics were used to evaluate differences among treatment groups for baseline scores, and descriptive and inferential statistics were used to compare the mean change from baseline RQLQ scores among and between the four treatment groups.

Safety measures included the incidence of potentially drug-related adverse events. Fisher's exact test was performed on pairs of treatments to detect differences in the number of patients with potentially drug-related adverse events overall and by body system.

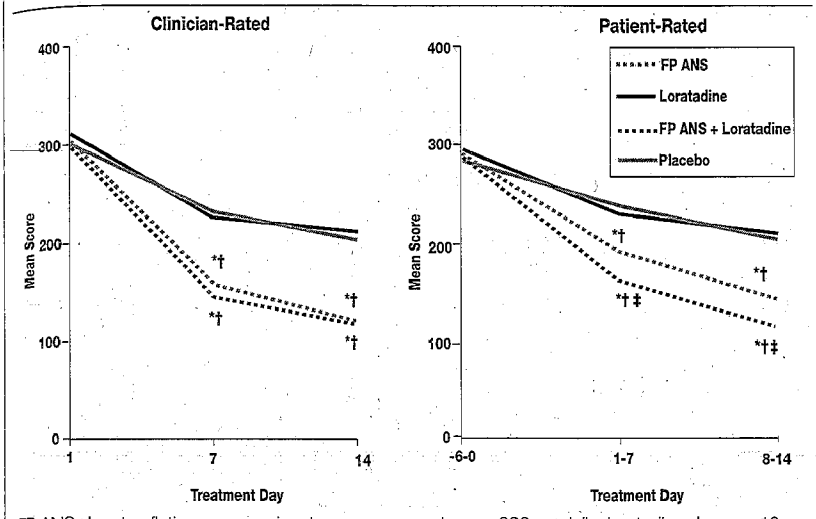
RESULTS

Patient Characteristics

Six hundred patients were enrolled in the study, and 569 (95%) completed it. Eight patients discontinued the study because of adverse events, 13 withdrew because of lack of efficacy, and seven withdrew for other reasons. Demographic characteristics and com-

FIGURE 1

Clinician-rated and patient-rated total nasal symptom scores after 1 and 2 weeks of therapy for seasonal allergic rhinitis.



FP ANS denotes fluticasone propionate aqueous nasal spray 200 µg daily; loratadine dosage, 10 mg once daily.
*P < .001 versus placebo.
†P < .001 versus loratadine.
‡P < .05 versus FP ANS for mean change from baseline.

TABLE 2

Baseline and Mean Change from Baseline at Day 7 and Day 14 for Clinician-Rated Nasal Symptom Scores

	Placebo Score (SE)	Loratadine Score (SE)	FP ANS Score (SE)	FP ANS + Lor Score (SE)
Total symptom score				
Baseline	302.4 (4.2)	313.3 (4.0)	304.9 (4.6)	304.9 (4.7)
Day 7	-71.0 (7.9)	-86.1 (8.6)	-149.0 (8.2) †‡	-158.0 (9.0) †‡
Day 14	-102.0 (8.8)	-102.0 (9.9)	-187.0 (8.5) †‡	-186.0 (9.4) †‡
Blockage				
Baseline	77.0 (1.4)	80.2 (1.2)	78.0 (1.4)	80.5 (1.4)
Day 7	-14.2 (2.2)	-16.8 (2.3)	-32.8 (2.2) †‡	-35.8 (2.5) †‡
Day 14	-20.0 (2.4)	-20.0 (2.6)	-42.5 (2.3) †‡	-42.6 (2.7)†‡
Discharge				
Baseline	81.3 (1.2)	85.0 (1.1)	82.8 (1.2)	83.0 (1.3)
Day 7	-18.1 (2.1)	-20.1 (2.4)	-38.5 (2.5) †‡	-40.7 (2.5) †‡
Day 14	-27.1 (2.5)	-26.9 (2.7)	-46.3 (2.6) †‡	-49.6 (2.7) †‡
Itching				
Baseline	76.0 (1.7)	76.3 (1.6)	74.4 (1.8)	73.6 (1.9)
Day 7	-19.9 (2.4)	-26.4 (2.5)	-38.6 (2.6) †‡	-41.0 (3.0)†‡
Day 14	-28.4 (2.6)	-29.3 (2.8)	-50.0 (2.5) †‡	-48.2 (2.7) †‡
Sneezing				
Baseline	68.1 (1.9)	71.7 (1.7)	69.7 (1.8)	67.8 (2.0)
Day 7	-18.9 (2.5)	-22.7 (2.7)	-38.8 (2.6) †‡	-40.1 (2.7)†‡
Day 14	-26.6 (2.7)	-26.3 (2.9)	-48.4 (2.6) †‡	-45.7 (2.9)†‡

Total symptom score is the sum of blockage, discharge, itching, and sneezing (maximum total possible = 400).
FP ANS denotes fluticasone propionate aqueous nasal spray; Lor, loratadine; SE, standard error.
† P <.05 versus placebo.
‡ P < .05 versus loratadine.

pliance rates were similar among the treatment groups (Table 1). Approximately 90% of the patients enrolled were recruited from the offices of primary care physicians or were under no medical care for their rhinitis symptoms. Less than 10% of the patients enrolled in the study were recruited from the practices of allergists who participated in the study.

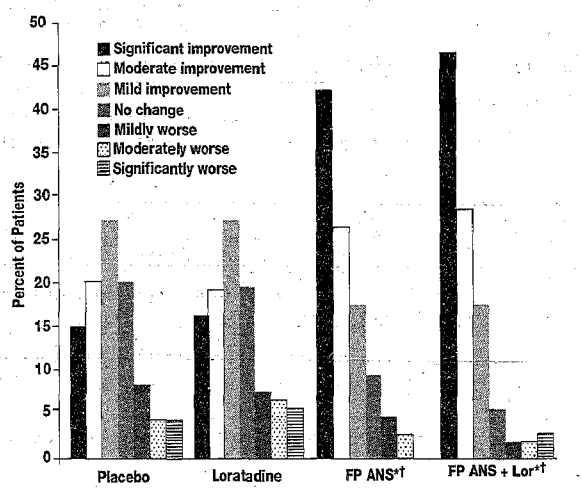
Efficacy Data

Nasal Symptoms Scores. At baseline, mean clinician-rated total nasal symptom scores were not significantly different between treatment groups. At clinic visits after 1 week of therapy (day 7), clinician-rated total nasal symptom scores were significantly lower (P < .001) in the FP ANS and FP ANS plus loratadine groups than in the loratadine only or placebo groups (Figure 1). At these timepoints, loratadine did not differ significantly from placebo aqueous nasal spray, and the FP ANS plus loratadine combination did not differ from FP ANS monotherapy (Table 2). After 2 weeks of therapy (day 14), total nasal symptoms were even further reduced in all treatment groups, with significantly lower scores in the FP ANS and FP ANS plus loratadine groups than in the loratadine or placebo groups. Again, loratadine did not differ significantly from placebo and there was no difference between the FP ANS plus loratadine combination and FP ANS monotherapy.

The data for clinician-rated individual nasal symptoms were similar to the total nasal symptom data (Table 2). At both the day 7 and day 14 assessments, scores in the FP ANS and FP ANS plus loratadine groups were significantly lower ($P \leq .05$) than loratadine alone and placebo group scores for blockage, discharge, itching, and sneezing. Clinician-rated scores for all individual nasal symptoms did not differ significantly between the FP ANS monotherapy and FP ANS plus loratadine combination treatment groups. Mean total and individual

FIGURE 2

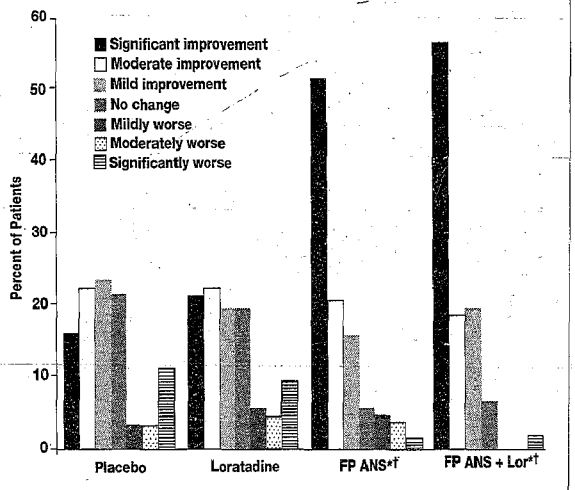
Clinician-rated overall response to therapy after 2 weeks of therapy for seasonal allergic rhinitis.



FP ANS denotes fluticasone propionate aqueous nasal spray 200 µg daily; loratadine dosage, 10 mg once daily.
*P < .001 versus placebo.
†P < .001 versus loratadine.

FIGURE 3

Patient-rated overall response to therapy after 2 weeks of therapy for seasonal allergic rhinitis.



FP ANS denotes fluticasone propionate aqueous nasal spray 200 µg daily; loratadine dosage, 10 mg once daily.
*P < .001 versus placebo.
†P < .001 versus loratadine.

nasal symptom scores for the loratadine and placebo treatment groups did not differ significantly at either the day 7 or day 14 evaluations.

The pattern of improvement observed in patient-rated total nasal symptom scores was similar to that reported in the clinician ratings, except that scores in the FP ANS plus loratadine combination group were significantly lower than those in the FP ANS monotherapy group at the evaluations on days 1 through 7 and days 8 through 14 (P values .006 and .017, respectively) (Figure 1). Individual nasal symptom score data generally conformed to a pattern similar to that seen for total nasal symptom scores; at days 1 through 7 and days 8 through 14, symptom scores in the FP ANS and FP ANS plus loratadine treatment groups were significantly lower than those in the loratadine only group (P <.05) and placebo group (P < .001). Individual nasal scores in the FP ANS plus loratadine group were significantly lower than those reported by patients in the FP ANS monotherapy group for nasal blockage, nasal discharge, and sneezing at days 1 through 7 and 8 through 14, and for nasal itching at days 1 through 7.

Clinicians' Overall Evaluation. In the clinician's overall evaluation at day 14, FP ANS and FP ANS plus loratadine were equivalent in efficacy and significantly more effective than placebo or loratadine only (P < .001)(Figure 2). No significant difference was observed between the loratadine and placebo treatment groups.

Patients' Overall Evaluation. Overall patient evaluations were in close agreement with overall clinical evaluations. FP ANS and FP ANS plus loratadine were significantly more effective than placebo or loratadine only (P < .001)(Figure 3), but were not significantly different from each other. No significant difference was observed between the loratadine and placebo treatment groups.

Patient-Rated Quality-of-Life Changes

At baseline, the mean global RQLQ scores and scores on each of the seven domains did not differ between or among the four treatment groups (Table 3). Significantly greater improvements in mean global RQLQ scores from baseline to day 14 were observed in the FP ANS treatment group than in the placebo and loratadine only treatment groups (P <. 001). There were no significant differences in the mean change from baseline RQLQ scores between the loratadine only and placebo groups. Significantly greater improvements were seen in the FP ANS plus loratadine group than in either the loratadine only or placebo treatment groups (P<.001); however, the RQLQ scores did not differ significantly between the FP ANS plus loratadine and FP ANS monotherapy groups.

Safety Data

The incidence and pattern of drug-related adverse events did not differ among the treatment groups.

TABLE 3

Mean Global and Individual Domain Scores on the Rhinoconjunctivitis Quality of Life Questionnaire

Variable	Placebo Score (SE)	Loratadine Score (SE)	FP ANS Score (SE)	FP ANS + Loratadine Score (SE)
Global score*				
Day 0	4.0 (0.1)	4.1 (0.1)	4.1 (0.1)	4.0 (0.1)
Day 14	-1.3 (0.1)	-1.3 (0.1)	-2.2 (0.1)†‡	-2.3 (0.1)†‡
Nasal symptom score				
Day 0	4.5 (0.1)	4.6 (0.1)	4.6 (0.1)	4.5 (0.1)
Day 14	-1.4 (0.1)	-1.4 (0.1)	-2.5 (0.1)†‡	-2.7 (0.1)†‡
Eye symptom score				
Day 0	3.8 (0.1)	3.8 (0.1)	3.8 (0.1)	3.8 (0.1)
Day 14	-1.2 (0.1)	-1.3 (0.1)	-1.9 (0.1)†‡	-2.0 (0.1)†‡
Activities score				
Day 0	4.4 (0.1)	4.6 (0.1)	4.4 (0.1)	4.4 (0.1)
Day 14	-1.5 (0.1)	-1.5 (0.1)	-2.3 (0.1)†‡	-2.5 (0.1)†‡
Practical problems score				
Day 0	4.2 (0.1)	4.5 (0.1)	4.4 (0.1)	4.3 (0.1)
Day 14	-1.3 (0.1)	-1.3 (0.1)	-2.5 (0.1)†‡	-2.7 (0.1)†‡
Sleep score				
Day 0	3.5 (0.1)	3.8 (0.1)	3.7 (0.1)	3.7 (0.1)
Day 14	-1.2 (0.1)	-1.2 (0.2)	-2.1 (0.1)†‡	-2.2 (0.1)†‡
Emotional score				
Day 0	3.5 (0.1)	3.5 (0.1)	3.5 (0.1)	3.4 (0.1)
Day 14	-1.3 (0.1)	-1.1 (0.1)	-1.9 (0.1)†‡	-2.1 (0.1)†‡
Other symptom score§				
Day 0	3.6 (0.1)	3.5 (0.1)	3.7 (0.1)	3.5 (0.1)
Day 14	-1.3 (0.1)	-1.1 (0.1)	-1.9 (0.1)†‡	-1.9 (0.1)†‡

FP ANS denotes fluticasone propionate aqueous nasal spray 200 µg once daily; loratadine dosage, 10 mg once daily. SE denotes standard error.
*The global score is defined as the mean of the individual domain scores on a scale from 0 (not troubled) to 6 (extremely troubled).
†$P < .05$ versus placebo based on mean change from baseline.
‡$P < .05$ versus loratadine based on mean change from baseline.
§Other symptoms are defined as those not involving the nose or eye (eg, fatigue, irritability, and tiredness).

From 5% to 8% of the patients in each treatment group experienced an event that was considered by the investigators to be related to the study therapy. The most frequently reported drug-related adverse events were blood in the nasal mucus (1% to 2% in active treatment groups and 3% in the placebo group), epistaxis (≤1% for all treatments), and xerostomia (≤2% for all treatments).

DISCUSSION

This is the first study to evaluate the efficacy, safety, and quality of life of patients with rhinitis following treatment with FP ANS in combination with loratadine. The results of this clinical trial indicate that in patients with seasonal allergic rhinitis, a 2-week treatment regimen with FP ANS 200 µg once daily is significantly more effective than loratadine 10 mg once daily or placebo. Adding loratadine to FP ANS offered no significant improvement over FP ANS alone with respect to clinician ratings, overall clinical evaluation, overall patient evaluation, and patient-rated quality of life. The combination was considered more effective according to some patient ratings. A lack of any significant differences between FP ANS and FP ANS in combination with loratadine also has been demonstrated in the analysis of pharmacoeconomic outcomes in this same patient population (reported elsewhere),[23] with FP ANS plus loratadine providing no advantages over FP ANS monotherapy with respect to patient-rated overall satisfaction with treatment, patient-perceived effectiveness with symptom relief, impact of treatment on patient work/school attendance, patient effectiveness with work/school activities, and interference of rhinitis symptoms with patient performance in leisure/recreation activities.

The superiority of FP ANS over loratadine for treating nasal symptoms was not unexpected. Four previous double-blind, double-dummy comparative trials have shown that FP ANS 200 µg once daily, administered to patients with seasonal allergic rhinitis for 4 weeks, significantly reduced nasal symptoms to a greater degree than loratadine.[8-11] With the exception of one study,[11] these clinical trials relied solely on subjective variables to assess efficacy. Jordana et al,[11] using portable peak inspiratory flowmeter measurements as an objective variable, found that FP ANS produced significantly greater nasal air flow than loratadine, and that this coincided with significantly less nasal blockage on waking and during the daytime. The effect of loratadine on nasal airflow has been shown to be the same as that of terfenadine,[24] an antihistamine that has proved over a 4-week period to be no more effective than aqueous nasal spray placebo and less effective

than FP ANS in improving nasal airflow.[14]

The superior quality-of-life results observed with FP ANS over loratadine in this 2-week clinical trial were similar to those previously reported by Mackowiak[25] in a 4-week clinical trial comparing the same FP ANS regimen with astemizole (10 mg daily), another nonsedating antihistamine, in patients with seasonal allergic rhinitis. Mackowiak found that RQLQ improvements paralleled improvements in the role–physical domain on the Short Form-36 quality-of-life test, which he also administered to his patient population.

To date, loratadine and other oral nonsedative antihistamines have proved no more effective than placebo aqueous nasal spray in placebo-controlled studies in which the active comparator was an intranasal corticosteroid,[8,12-15,26] whereas they have demonstrated superior efficacy to placebo tablets in placebo-controlled studies in which the active comparator has been another oral antihistamine.[27-30] This result may be expected, because an intranasal aqueous nasal spray placebo is capable of washing away secretions, inflammatory cells, and mediators.[31,32] For this reason, aqueous nasal spray placebos exert some therapeutic activity and are not true placebos.

The clinical efficacy and safety of the combined use of an intranasal corticosteroid and an oral antihistamine combination have been studied previously in several clinical trials.[17-20,33] In two clinical trials conducted over 2 to 14 weeks, the addition of recommended regimens of intranasal beclomethasone dipropionate to regimens of terfenadine 60 mg twice daily or astemizole 10 mg once daily[18] prompted significant improvement in nasal symptoms over the respective antihistamine monotherapy regimens. In a 7-day study, the addition of loratadine 10 mg once daily to a beclomethasone dipropionate regimen resulted in significantly greater nasal and ocular symptom relief than was achievable with beclomethasone dipropionate monotherapy.[17] However, in a 2-week study,[33] the addition of loratadine 10 mg once daily to a regimen of intranasal mometasone furoate 200 µg once daily failed to provide any significant additional relief of total rhinitis symptoms than was attainable with mometasone monotherapy. To date, only one other clinical trial[20] has compared combined use of FP ANS and an oral antihistamine with FP ANS monotherapy. This study, which was conducted over an 8-week period in patients with seasonal allergic rhinitis, did not use antihistamine monotherapy as an active control. As in the present study, the addition of an antihistamine (cetirizine 10 mg once daily) to a regimen of FP ANS 200 µg once daily had no effect on clinical efficacy or safety. Although adding an antihistamine to a beclomethasone dipropionate regimen results in further symptom improvement, supplementing an FP ANS regimen with an antihistamine regimen provides little additional benefit.

It has been suggested that the results of short-term studies may differ from those of longer-term trials and that this may be a limitation of the 2-week treatment period in this study. It was conducted in a short but well-defined season of a pollen similar to ragweed in that it produces moderate to severe symptoms of allergic rhinitis. One advantage of this design is that it allows for large numbers of patients affected by the same pollen to be studied within the same period. A study of longer duration may result in a decrease in symptoms at the end of the treatment period that could be attributed to the decrease in exposure to allergen as the allergy season ends, rather than to the effect of study therapy.[34]

The most commonly reported potentially drug-related adverse events in this study included various forms of nasal bleeding, a frequent occurrence with use of intranasal sprays. However, reports of blood in nasal mucus were low, generally mild, and similar for both FP ANS and loratadine. Xerostomia was also commonly reported, which is not unusual with antihistimine use. There was no apparent increase in the incidence of adverse events with the combination of FP ANS and loratadine.

For the treatment of seasonal allergic rhinitis, FP ANS is superior to loratadine alone and to placebo, and adding loratadine to FP ANS does not confer meaningful additional benefit.

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Budesonide and terfenadine, separately and in combination, in the treatment of hay fever

Richard J. Simpson, MB, ChB

Background: While hay fever is a very common experience, its treatment in primary care setting has been little reported in controlled studies.

Objective: This study sought to evaluate the patient's assessment of efficacy of an intranasal steroid spray (budesonide) alone or in combination with an antihistamine (terfenadine) against terfenadine alone or placebo alone.

Methods: A double-blind parallel group, placebo-controlled trial design was used, comparing the four groups. Each group used an active or placebo spray and active or placebo tablets. Symptom scores were recorded daily in diaries over a 21-day period.

Results: Overall assessment of efficacy by the 106 patients was significantly greater ($P < .05$) for budesonide versus terfenadine or placebo alone. There was a 40% placebo response. Budesonide was more effective than terfenadine for all individual symptom scores, particularly nasal blockage, against which terfenadine was ineffective. Adverse effects were mild and transient for all groups.

Conclusions: Budesonide alone is a highly effective treatment for hay fever with few side effects.

INTRODUCTION

It has been estimated that 10% to 17% of North Americans experience allergic rhinitis[1] and that hay fever, an allergy to pollen resulting in rhinitis and conjunctival symptoms, is one of the most common forms of the disease. Following exposure to the allergen, IgE-mediated stimulation of mast cells results in the release of allergy mediators such as histamine, which cause increased vascular permeability, mucous secretion, and stimulation of neural reflexes (resulting in pruritus and sneezing). Late-phase inflammatory reactions[2] include the attraction and infiltration of inflammatory cells, such as mast cells, eosinophils, basophils, neutrophils and lymphocytes into the mucosa.[3] The increased irritability of the nose observed during the allergy season is largely due to this inflammatory reaction. The result of these processes is the characteristic nasal symptoms of hay fever including pruritus, nasal congestion, runny nose, and sneezing.

Treatment of hay fever includes antihistamines, decongestants, sodium cromoglycate,[4] topical (intranasal),[5] or systemic[6] steroids and immunotherapy.[7] Antihistamines are well-established in the treatment of hay fever, reflecting the role of histamine release in its pathogenesis, but their usefulness has until recently been limited because of their anticholinergic, central nervous system and sedative side effects,[8] which are potentiated by sedatives, hypnotics, antidepressants, and alcohol. More recent H_1-receptor antagonists produce a much lower incidence of sedation[8]; however, terfenadine, the most widely prescribed antihistamine, and a second compound in this group, astemizole, have both been shown to cause ventricular arrhythmias in overdose[9,10] or when used in combination with erythromycin or other macrolide antibiotics and the antifungal preparation ketoconazole.[11] Although clinical trials have shown antihistamines to relieve symptoms such as sneezing, itchy nose and runny nose, in general they are not thought to be effective in relieving nasal blockage, and thus may be formulated in combination with a decongestant.[12]

Systemic treatment with corticosteroids can be used in hay fever, but is usually reserved for the most severe and persistent cases because of the risk of adverse effects associated with the long-term use of this type of therapy.[13] Intranasal corticosteroids, on the other hand, provide one of the most potent therapies for hayfever[7,14] and their local mode of application avoids the adverse effects associated with systemic corticosteroids while at least equalling their efficacy.[15] They also lack the sedative effects of antihistamines. The limitations of intranasally applied steroids are that, due to their localized action, they may not be effective in controlling eye symptoms and that some patients experience nasal irritation or mild epistaxis as a result of using them.[16]

In the current study, the efficacy of intranasal budesonide, a corticosteroid preparation, was compared with that of terfenadine and a combination of the two in the treatment of hay fever, in a double-blind, parallel-group, placebo-controlled study.

MATERIALS AND METHODS

Patients

Men and women aged 15 years or

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over at entry were recruited from a primary care setting into the trial. All patients had experienced symptoms of hay fever between May 1 and August 31 for at least 2 years preceding the study, and at the time of recruitment were suffering from two or more of the following symptoms: blocked nose, runny nose, itching nose, or sneezing. Any patients who were taking oral corticosteroids, were suffering from respiratory tract infections (bacterial, viral, or fungal) at the time of recruitment, had taken desensitization therapy during the previous 12 months or who suffered hay fever symptoms outside the specified period were excluded from the study, as were pregnant women.

The nature and purpose of the study were explained to the patients in both oral and written form, and their written consent to participation in the study was obtained. The study was approved by the local ethics committee and was performed in accordance with the Declaration of Helsinki.

Study Procedures

Patients visited their general practitioner on entry to the study, at which time demographic details and the patient's assessment of hay fever symptoms during the previous 24 hours were recorded. The symptoms assessed were blocked nose, runny nose, itchy nose, sneezing bouts, runny eyes, and sore eyes. Symptoms were scored using a 4-point system where 0 = no symptoms, 1 = mild symptoms (present but not troublesome), 2 = moderate symptoms (some discomfort experienced), and 3 = severe symptoms (discomfort experienced during most of the waking hours). A minimum score of 2 was required for entry into the study.

On entry to the study, patients were randomized to one of four parallel groups receiving (1) intranasal budesonide (Rhinocort, Astra Draco AB, Lund, Sweden), 200 μg bid, plus terfenadine (Triludan, Marion Merrell Dow, Uxbridge, Middlesex, UK), 60 mg bid; (2) terfenadine, 60 mg bid, plus a placebo nasal spray (identical to the budesonide nasal spray but delivering propellant and lubricant only); (3) intranasal budesonide, 200 μg bid, plus placebo tablets identical in appearance to the terfenadine tablets; and (4) placebo nasal spray plus placebo tablets. Patients were instructed to deliver two puffs from the nasal spray into each nostril morning and evening, and to take one tablet in the morning and one in the evening, for 21 days. The use of other medications for hay fever, particularly oral corticosteroids and antihistamines, was forbidden but in the event of troublesome eye symptoms patients were permitted to use xylometazoline or metazoline eye drops.

Patients were supplied with diary booklets and asked to record, at the end of each day, symptom scores experienced during the day for blocked nose, runny nose, sneezing, itchy nose, runny eyes and sore eyes, using the same scoring system as on entry to the study. The number of eye drops used during each 24 hours was also recorded, as were any comments about the symptoms or treatment.

Patients visited their general practitioner after seven days' treatment, and were reminded of their option to withdraw from the study if the previous week's treatment had been ineffective. The diary booklets were checked for accuracy and completeness, and any comments made by the patients were recorded. At the final visit, after 21 days of treatment, comments by either the patient or the physician were recorded, any inconsistencies in the diary booklets clarified, and patients were asked to make a global assessment of the efficacy of treatment according to a 4-point scale where 0 = ineffective, 1 = slightly effective, 2 = noticeably effective, and 3 = very effective.

Statistical Analysis

Mean weekly symptom scores for each patient who completed the study were determined from the diary booklets and overall means for each treatment group calculated from these. One-way analysis of variance (using pooled variance) was carried out on the 3-week treatment mean, the last week of treatment and weeks 1, 2, and 3 separately. Where statistically significant treatment differences were indicated by the F-ratio, linear contrasts were used to determine the statistical significance of individual treatment differences.

Global assessment and eye drop use were subjected to Kruskal-Wallis one-way analysis of variance followed by the Wilcoxon rank sum-W test where appropriate.

RESULTS

Efficacy

One hundred forty-three patients reporting to their general practitioner with symptoms of hay fever were recruited into the study. Records from six patients were unusable because of confused numbering (five patients) and lost data (one patient). Twenty patients withdrew because of lack of treatment efficacy, the majority of these (12) being in the placebo group A further three patients withdrew as a result of adverse events and five patients failed to return for assessment on one or more occasions. Three patients severely violated the protocol during the trial, and were withdrawn. Table 1 shows demographic characteristics and symptom severity at baseline for the 106 patients who were evaluated for efficacy. On entry to the study, the four treatment groups were well matched with respect to symptom severity and demographic characteristics, with the exception of the placebo group which had a higher proportion of men than the other groups.

Figure 1 shows the results of the patients' overall assessment of the efficacy of treatment, whereas Figure 2 shows the analysis of individual symptom scores derived from

Table 1. Demographic Characteristics and Baseline Mean Symptom Scores (± SD) of Patients Assessed for Efficacy

	Placebo	Treatment Group		
		Budesonide	Terfenadine	Budesonide + Terfenadine
Demographic characteristics				
Number of patients	21	30	23	32
Men/women (%)	71/29	43/57	53/47	41/59
Age, yr (mean ± SD)	27.7 (± 12.2)	26.8 (± 12.4)	29.7 (± 11.7)	25.7 (± 7.8)
Mean symptom scores				
Blocked nose	1.6 ± 1.1	1.9 ± 0.9	1.6 ± 1.2	1.8 ± 1.0
Sneezing bouts	2.3 ± 0.6	2.1 ± 0.8	1.9 ± 1.1	1.9 ± 0.7
Nasal itching	1.1 ± 1.1	1.2 ± 1.0	1.4 ± 1.1	1.2 ± 1.1
Runny nose	2.0 ± 0.9	1.9 ± 1.1	1.7 ± 1.2	1.6 ± 0.8
Sore eyes	1.8 ± 1.2	1.8 ± 1.1	1.7 ± 1.1	1.3 ± 1.3
Runny eyes	1.5 ± 1.3	1.5 ± 1.2	1.3 ± 1.2	1.3 ± 1.1

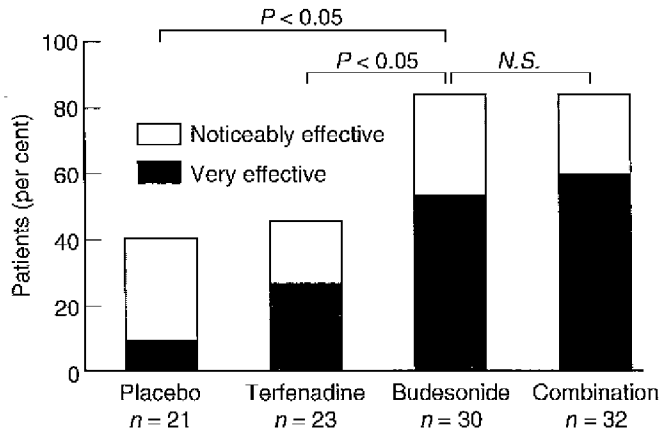

Figure 1. Patients' overall assessment of the efficacy of treatment. Percentage of patients in each treatment group who reported the global efficacy of their treatment at week 3 as noticeably effective or very effective, with statistical comparison between groups (Wilcoxon rank sum-W test). NS = not significant.

patient booklets. Forty percent of patients in the placebo group and 46% of patients treated with terfenadine alone rated the overall efficacy of their treatment as noticeably effective or very effective, in comparison to 85% of patients receiving budesonide alone or in combination with terfenadine (Fig 1). A comparison between groups showed statistically significant ($P < .05$) differences in the patients' overall assessment of treatment efficacy between budesonide versus terfenadine and budesonide versus placebo, but no significant difference was observed between terfenadine versus placebo or between budesonide alone versus budesonide in combination with terfenadine.

Figure 2 shows that treatment with terfenadine alone resulted in statistically significant ($P < .05$) reductions in symptom scores for runny nose and itchy nose as compared with placebo. Terfenadine, however, had no effect on nasal blockage. Treatment with budesonide alone reduced all mean nasal symptom scores as compared with placebo, the differences being statistically significant ($P < .05$). Budesonide also reduced mean symptom scores more than terfenadine for all nasal symptoms, the difference being statistically significant in the case of nasal blockage. The combination of budesonide and terfenadine produced symptom scores similar to budesonide alone for blocked nose, itchy nose and runny nose, and reduced the mean sneezing score by more than either terfenadine or budesonide alone, the differences being statistically significant ($P < .05$). Figure 3 shows changes in mean total nasal symptom scores during the first week of treatment. Terfenadine used alone achieved its maximum efficacy within one to two days. After two to three days, the symptom scores with budesonide were lower than with terfenadine, and symptoms continued to improve over days 3 to 7. Budesonide and terfenadine combination treatment produced a similar effect to treatment with budesonide alone.

Analysis of diary records of eye symptoms and eye drop use revealed that there were no statistically significant differences in eye symptom scores between treatment groups, although the scores tended to be lower in the active treatment groups than in the placebo-treated patients. Eye drop use in all groups remained relatively constant throughout the study; although use in the budesonide group was higher than that in the terfenadine group, this did not reach statistical significance.

Safety

The six patients whose records were lost or confused were excluded from the safety assessment. Nineteen of the 137 patients evaluated for safety experienced adverse events. These events were generally mild and transient, the most common being local effects related to use of the nasal spray, such as sneezing and nasal irritation after its use. One patient treated with combined budesonide and terfenadine experienced palpitations one hour after taking the tablets, as she had previously when taking chlorpheniramine maleate (Piriton) tablets. Three patients

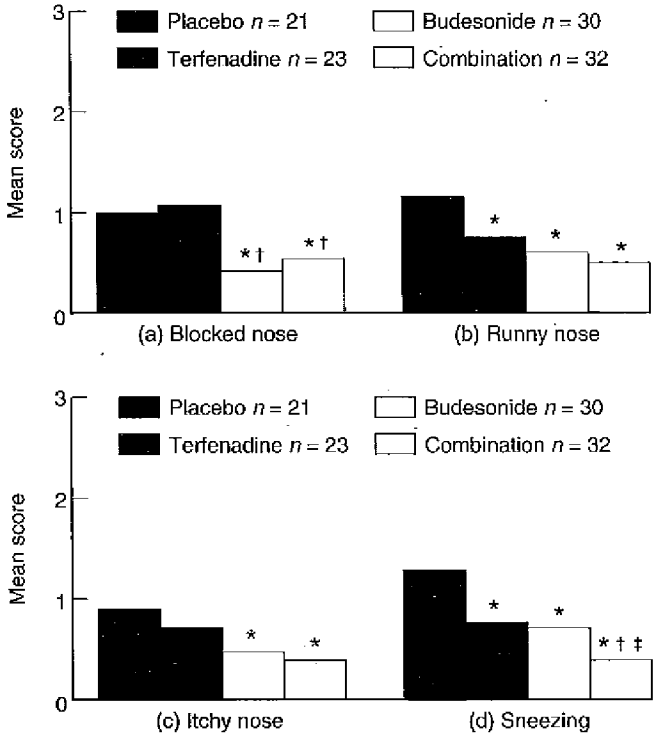

Figure 2. Assessment of nasal symptom scores at week 3 as derived from patients' diary booklets. * Statistically significant difference versus placebo ($P < .05$). † Statistically significant difference versus terfenadine ($P < .05$). ‡ Statistically significant difference versus budesonide ($P < .05$).

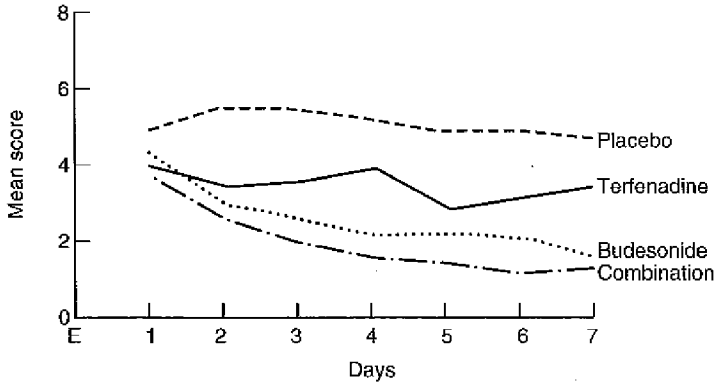

Figure 3. Changes in mean total nasal symptom scores in each treatment group during the first week of treatment.

withdrew from the study as a result of adverse events; these were one placebo-treated patient who suffered from nausea after taking the tablets, one budesonide-treated patient who suffered from fatigue, and one patient on combination therapy who experienced intolerable sneezing and headache after using the nasal spray. A summary of adverse events is shown in Table 2.

DISCUSSION

The current study demonstrates that both intranasal budesonide and oral terfenadine were more effective than placebo in the treatment of hay fever symptoms. This confirms previous studies with budesonide[17] and terfenadine.[18] Budesonide, however, was found to control all nasal symptoms of hay fever whereas terfenadine did not significantly affect nasal blockage. The lack of efficacy of terfenadine against nasal blockage has been observed in other studies[19,20] and is likely to be clinically significant, as 59% of patients in the present study complained of nasal blockage. Scores for eye symptoms were similar on treatment with budesonide or terfenadine, separately or in combination, and lower than scores in the placebo group, although the difference was not statistically significant. More xylometazoline or metazoline eye drops were used by patients in the budesonide group, which may indicate better control of eye symptoms with terfenadine.

Budesonide was found to be considerably more effective than terfenadine, according to the overall assessment of treatment effect by the patients. In the budesonide group, 85% of patients rated their treatment as noticeably effective or very effective compared with 46% in the terfenadine group and 40% in the placebo group, a level of placebo response that emphasizes the importance of adequate control groups in hay fever studies. Indeed, placebo nasal spray can produce a substantial reduction in symptoms.[21] Although the scores for individual nasal symptoms tended to be lower with combined budesonide and terfenadine treatment than with either drug used alone, the global assessments of combination therapy and budesonide alone were very similar, indicating that the lower scores for individual symptoms were not perceived by patients as improvements in their overall condition. Terfenadine, budesonide, and combination therapy all had a good safety profile; adverse effects were minor and infrequent with all treatments, and patients on active treatments expe-

Table 2. Number of Patients Reporting Adverse Events

Event	Placebo (n = 36)	Terfenadine (n = 29)	Budesonide (n = 35)	Budesonide + Terfenadine (n = 37)
Nasal adverse events				
Sneezing after use of				
Nasal spray	3	2	2	2
Nasal irritation*	1	0	1	1
CNS adverse events				
Headache	0	0	0	2
Fatigue	0	0	2	0
Other adverse events				
Nausea	1	0	1	0
Dry mouth	0	0	0	1
Palpitations	0	0	0	1

* Described as stinging, itching, or irritation.

rienced no more adverse effects than those taking placebo.

The lack of efficacy of terfenadine and other antihistamines in the treatment of nasal congestion in hay fever may be an indication of the inflammatory nature of the late-phase response in allergic rhinitis; anti-inflammatory agents such as corticosteroids could be considered as a more rational solution than antihistamines for the nasal symptoms of hay fever, especially given the excellent safety profile when applied intranasally. Budesonide has been shown to be more effective than beclomethasone dipropionate in the treatment of hay fever[22,23] and thus represents an excellent choice for the treatment of this condition.

In conclusion, symptoms of runny or itchy nose and sneezing could be improved by terfenadine or budesonide administered alone or in combination, but blocked nose was only improved when budesonide was included in the treatment regime. Budesonide, alone or in combination with terfenadine, was perceived by patients as being significantly more effective in alleviating symptoms than terfenadine alone.

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LONG-TERM TREATMENT OF CHILDREN WITH INHALED BUDESONIDE IMPROVES CONTROL OF ASTHMA WITH NO ADVERSE EFFECT UPON GROWTH

To evaluate effects of inhaled budesonide the authors studied 278 children with mild or moderate asthma at initial ages of 3 to 11 years. After having been followed for 1–3 years during which they received no corticosteroid for more than 2 weeks per year, 216 children received inhaled budesonide, 800 μg/day via Nebuhaler for 6 to 8 weeks. After establishment of optimal control the dosage was gradually by reduced 25% at monthly intervals as tolerated. These children continued to receive inhaled budesonide for 2 to 6 years (mean 3.7 years). Sixty-two children whose parents did not want them to receive an inhaled corticosteroid because of fear of adverse effects served as controls and were followed for 3 to 7 years (mean 5.2 years).

During treatment with budesonide the mean daily dose decreased from 710 to 430 μg with no evidence of tachyphylaxis. The number of annual hospital admissions for acute severe asthma decreased from 0.03 to 0.004 per child ($P < .001$) and FEV_1 improved significantly as compared with both the run-in period and the control group. There was a significant relationship between the duration of asthma at initiation of treatment with budesonide and the annual increase in FEV_1 during treatment with budesonide. Children who started treatment more than 5 years after the onset of asthma had significantly lower FEV_1 (96% predicted) after 3 years of treatment with budesonide than those who received budesonide within the first 2 years after onset of asthma (101% predicted, $P < .05$). There were no significant changes in growth velocity or weight gain during treatment with budesonide as compared with the run-in period or controls.

These data indicate inhaled budesonide at doses of 400 μg per day does not inhibit linear growth in most children with mild or moderate asthma. Early treatment with inhaled corticosteriod may be more effective than treatment more than 5 years after the onset of asthma.

–RMS

Agertoft L, Pedersen S. Effects of long-term treatment with an inhaled corticosteriod on growth and pulmonary function in asthmatic children. Respir Med 1994;88:373–81.

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A comparison of the anti-inflammatory properties of intranasal corticosteroids and antihistamines in allergic rhinitis

Allergic rhinitis manifests itself clinically due to the local release of mediators from activated cells within the nasal mucosa. Treatment strategies aim either to reduce the effects of these mediators on the sensory neural and vascular end organs, or to reduce the tissue accumulation of the activated cells that generate them. Corticosteroids intervene at a number of steps in the inflammatory pathway, and, by reducing the release of cytokines and chemokines, inhibit cell recruitment and activation. These effects are evident both *in vivo* and *in vitro*. While antihistamines also have some anti-inflammatory effects *in vitro*, these require higher concentrations than with corticosteroids and are not consistently reproduced *in vivo*. In addition, although antihistamines and corticosteroids might appear to have complementary mechanisms of action, clinical trials suggest that their co-administration does not confer any additional long-term benefits compared with that achieved with corticosteroids alone. Topical corticosteroids are therefore the preferred anti-inflammatory therapy for persistent allergic rhinitis.

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Introduction

Allergic rhinitis is the clinical manifestation of the local release, within the nasal mucosa, of mediators from activated inflammatory cells (1). Immunohistochemical studies of nasal biopsies taken from patients with allergic rhinitis show an accumulation within the epithelium of eosinophils, basophils, and mast cells (2–4), which are believed to be the primary effector cells in this condition, while nasal lavage reveals elevated levels of eosinophil cationic protein and tryptase in seasonal and perennial allergic rhinitis, indicative of cell activation (5).

Treatment for allergic rhinitis is directed toward reducing either the tissue accumulation of these activated cells or the end-organ effects of the released mediators. The two most important classes of pharmacologic agents used to achieve these aims are, respectively, topical corticosteroids and H_1-antihistamines. While H_1-antihistamines are clearly effective in relieving symptoms, particularly those associated with sensory neural stimulation, it has been proposed that many drugs within this class have more extensive actions, modifying the inflammatory process in addition to inhibiting the H_1-receptor-mediated end-organ effects of histamine. As such, H_1-antihistamines might be potentially considered an alternative prophylactic therapy to topical corticosteroids in rhinitis. To address this consideration, this paper briefly reviews the mechanisms involved in airways inflammation in allergic rhinitis and examines the *in vitro* and *in vivo* evidence for the relevant anti-inflammatory potential and effects of these two classes of pharmacologic agents.

Allergic airways inflammation

The major pathways involved in allergic airways inflammation are shown in Fig. 1. In addition to IgE-dependent activation of mast cells inducing mediator release, activated mast cells and T cells produce TH_2 cytokines, which, in turn, activate both endothelial and epithelial cells (1). Endothelial activation results in the expression of endothelial adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) and, more importantly, vascular cell adhesion molecule-1 (VCAM-1). While both these adhesion molecules are potentially involved in tissue-cell recruitment (6), the interaction between VCAM-1 and the ligand VLA-4 is more specific for allergic inflammation, being involved not only in eosinophil adherence but also in basophil and lymphocyte endothelial interactions. The directed movement of cells through the tissue toward the nasal lumen, once transendothelial migration has taken place, is dependent upon cell–cell contact and the local release of chemokines. Epithelial activation is associated with the generation and release of a number of chemokines – such as regulated on activation, normal T-cell expressed and secreted (RANTES), macrophage inflammatory protein (MIP)-1α, monocyte chemotactic protein

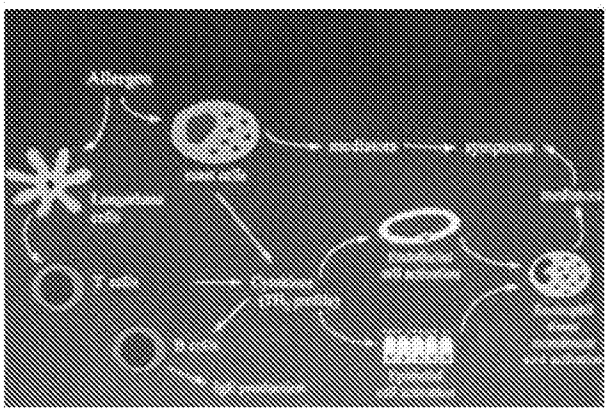

Figure 1. Allergic airways inflammation.

(MCP)-1, interleukin-8 (IL-8), and eotaxin – which are chemoattractants for eosinophils, mast cells, lymphocytes, neutrophils, and basophils, and direct the migration of these cells toward the epithelium and nasal airway lumen (7). Epithelial activation can thus account for the specific accumulation of mast cells, eosinophils, basophils, and T cells within the epithelium in allergic rhinitis.

It follows that therapy which reduces either the expression of these chemokines or the cytokines associated with endothelial and epithelial activation will diminish the recruitment of these effector cells and thus decrease the availability of mediators to induce symptom expression.

Cytokine and chemokine expression is regulated by transcription factors such as nuclear factor kappa B (NFκB), AP-1, and NF-AT (8). In the unactivated cell, transcription factors exist in an inactive form, and cell stimulation results in their activation with a resultant upregulated expression of cytokine and chemokine messenger RNA (mRNA). For example, NFκB exists as a dimer bound to an inhibitory protein, I kappaB (IκB), within the cytoplasm (9). When exposed to an activation stimulus, phosphorylation of the inhibitory protein leads to loss of binding, and the dimer dissociates from the inhibitory protein and translocates to the nucleus. Once there, it interacts with the DNA, resulting in a directed increase in gene expression and upregulation of specific cytokine (e.g., IL-1 and TNF-α) and chemokine (e.g., RANTES and eotaxin) synthesis. The transcription factor NFκB also controls the synthesis of adhesion molecules (such as VCAM-1) and enzymes (such as inducible nitric oxide synthase [iNOS]) of relevance to allergic nasal inflammation.

Corticosteroids

Corticosteroids act by modifying the ability of transcription factors to up-regulate gene expression (10). Thus, by acting very early in the inflammatory pathway, corticosteroids can prevent the cascade of events associated with cell recruitment and activation, and, ultimately, clinical disease expression.

The glucocorticoid molecule enters the cell and binds to the cytoplasmic glucocorticoid receptor, displacing the associated heat-shock proteins. The glucocorticoid/glucocorticord receptor complex can either bind to the transcription factors themselves within the cytoplasm, thereby preventing their interaction with DNA and thus indirectly blocking their effects on gene expression, or translocate to the nucleus and bind as a dimer to the DNA. This direct interaction with DNA modifies gene transcription, down-regulating the production of pro-inflammatory proteins or up-regulating the generation of anti-inflammatory ones. This latter action may require higher concentrations than the down-regulatory activity. Corticosteroids thus have both direct and indirect effects in inhibiting transcription factor-induced gene expression.

In vitro studies

Studies with corticosteroids *in vitro* have shown that this class of drug has potent effects on T cells, inhibiting their stimulated proliferation and synthesis of TH_2 cytokines at low concentrations (11–13). In this respect, fluticasone propionate is the most potent of the currently available topical corticosteroids, having an IC_{50} (inhibitory concentration producing a 50% reduction in the stimulated response) in the range of 10^{-10} M (13, 14). In addition to this inhibitory effect on T cells, fluticasone propionate inhibits the release of IL-4, IL-6, IL-8, and TNF-α from stimulated mast cells with an IC_{50} of <1 nM (15). The IC_{50} for inhibiting the release of TNF-α and GM-CSF from the stimulated epithelium are 0.1 and 1.0 nM, respectively (16). Epithelium-generated IL-6 and IL-8 are less sensitive to the effects of fluticasone, with IC_{50} of 5 and 10 nM, respectively (16).

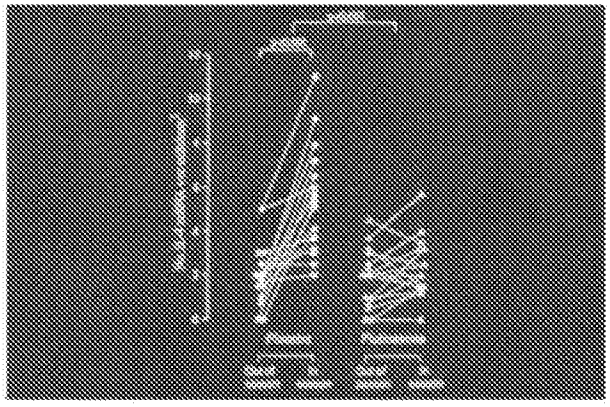

Figure 2. Influence of fluticasone propionate on mucosal IL-4 mRNA in nasal biopsies in seasonal allergic rhinitis (Cameron et al. [17]).

In vivo studies

Topical corticosteroid therapy influences many aspects of the allergic mucosal response. Much of the published literature concerns fluticasone propionate, and, to a lesser extent, budesonide. Fluticasone propionate significantly blunts the seasonal increases in the expression of mRNA for both IL-4 (Fig. 2) (17) and IL-5 (18), in nasal mucosal biopsies in seasonal allergic rhinitis. In addition, prophylactic treatment with fluticasone propionate, as compared to placebo, prevents the pericellular expression of the activated and secreted form of IL-4 (as demonstrated by the number of immunoreactive 3H4 + cells) on nasal mucosal mast cells in seasonal rhinitis (Fig. 3) (19). Thus, fluticasone propionate downregulates both IL-4 and IL-5 gene expression as well as the active secretion of IL-4 within the nasal mucosa. These are key cytokines in regulating endothelial VCAM-1 expression and, consistent with this, fluticasone propionate has also been shown to inhibit the seasonal increase in endothelial VCAM-1 expression (20). This action, along with a reduction in IL-5, a cytokine known to stimulate the proliferation and differentiation of eosinophil progenitor cells within the bone marrow, can account for the decrease in eosinophils within the nasal mucosa and lumen with topical corticosteroid therapy in rhinitis (20, 21).

This inhibitory effect on inflammatory cell accumulation in allergic rhinitis will also be promoted by the downregulation, by corticosteroids, of chemokine synthesis by the epithelium. Fluticasone propionate has been shown to reduce significantly the levels of IL-1β, MIP1α, RANTES, and GM-CSF recovered from nasal lavage after allergen challenge (Fig. 4) (22), indicating inhibition of epithelial activation. This action may underlie the inhibitory effect of fluticasone propionate in preventing the seasonal accumulation of mast cells within the epithelium in grass pollenosis (Fig. 5).

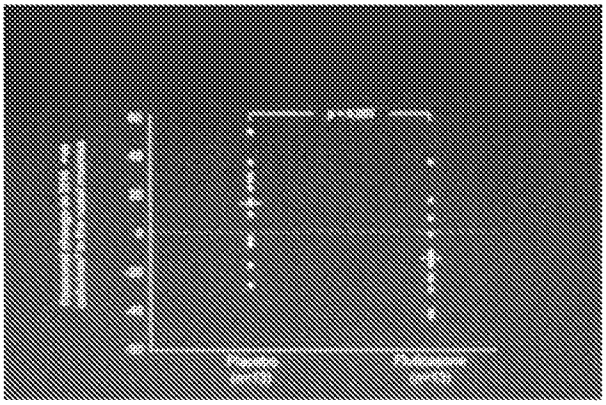

Figure 3. Influence of prophylactic fluticasone propionate on IL-4 secretion by mast cells in seasonal allergic rhinitis (Bradding et al. [19]).

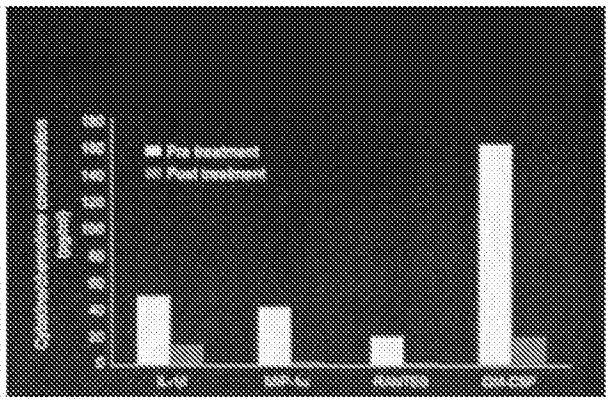

Figure 4. Nasal lavage chemokine levels: influence of fluticasone propionate (Weido et al. [22]).

Thus, fluticasone propionate modifies a number of steps in the inflammatory pathway: it blocks cytokine and chemokine generation, endothelial and epithelial cell activation, and the tissue recruitment and activation of mast cells and eosinophils. It follows that the fewer the number of these primary effector cells, the lower the amount of inflammatory mediators produced and, as a consequence, the fewer the nasal symptoms.

Antihistamines

Since many rhinitis symptoms are mediated by histamine, antihistamines offer a therapeutic alternative to corticosteroids. With short-term therapy, H_1-antihistamines are most effective at reducing the neurally mediated symptoms of itch, sneeze, and rhinorrhoea (23). This can be attributed to end-organ receptor blockade. There is, however, an indication that a number of these agents also have the potential for antiallergic activity that, theoretically, may increase their spectrum of clinical effectiveness.

In vitro studies

Studies undertaken *in vitro* show that H_1-antihistamines modify mediator release from mast cells and basophils (24, 25). These investigations reveal that, for most traditional antihistamines, the antiallergic activity requires higher concentrations than the H_1-antihistaminic activity. For example, the pA_2 value to inhibit anti-IgE induced mast cell degranulation is about 2 logs lower; i.e., the dose required to abolish the allergic response is approximately 100-fold higher than for the H_1-antihistaminic activity (24). The exception is oxatomide, which has similar antiallergic and antihistamines pA_2 values (26). Thus, for these effects to be fully evident *in vivo*, most H_1-antihistamines would have to be administered at doses higher than generally tolerated, due to their sedative effects.

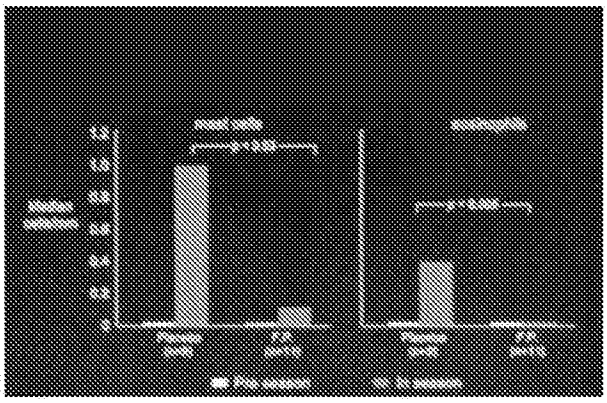

Figure 5. Epithelial eosinophil and mast-cell accumulation in seasonal allergic rhinitis: influence of prophylactic fluticasone propionate, 200 μg once daily (Bradding et al. [19]).

For some more recently introduced non-sedating antihistamines, including terfenadine, cetirizine, and loratadine, IC_{50} values for inhibition of anti-IgE- or allergen-induced histamine release are in the 10 μM range (27, 28). In other words, the inhibition of histamine release by these agents requires a concentration at least 1000 times higher than that those of fluticasone propionate required to inhibit cytokine or chemokine release. The "antiallergic" effects are considered to be independent of the H_1-receptor antagonistic activity and to be related to nonspecific cell membrane stabilization due to ionic association with cell membranes. This leads to modification of ion transport and membrane-associated enzyme activity (29–31).

In addition, several H_1-antihistamines have been shown to modify *in vitro* the epithelial expression of the adhesion molecule ICAM-1. Both terfenadine and cetirizine have been found to reduce the expression of ICAM-1 on epithelial cell lines *in vitro* (32).

In vivo studies

Antihistamines may exert their effects either directly, by inhibiting end-organ effects, or indirectly by inhibiting mast cell degranulation. This has been investigated in allergen-challenge models *in vivo*, with nasal lavage to measure postchallenge mediator levels. Pretreatment with standard doses of antihistamines, as compared to placebo, has been shown to decrease the recovery of mediators following allergen challenge (33). Overall, however, the effects of the various agents appear to be somewhat variable. Thus, azelastine, cetirizine, and ketotifen (34–36) have no effect on histamine release, although a decreased recovery of leukotrienes has been reported with both azelastine and cetirizine (34, 35). Conversely, several studies show decreased histamine release with loratadine and terfenadine (37–39), but no change in the recovery of leukotrienes. None of these drugs appear to have a consistent effect on the subsequent eosinophil accumulation in the allergen challenge model (40). The interpretation of these findings is also complicated by the report that factors, including histamine, which increase plasma protein exudation, increase mediator recovery in nasal lavage (41). Thus, inhibition of a histamine-related increase in vascular permeability after allergen challenge, due to the H_1-receptor blockade on the endothelial surface, could reduce mediator recovery in nasal lavage and be interpreted as reflecting an "anti-allergic" effect.

An antihistamine that decreased leukotriene production might be expected to have a broader clinical profile than one with antihistamine activity alone. In clinical studies, however, agents that inhibit leukotriene production in the allergen challenge test have similar clinical benefits to those that do not (42, 43), raising some doubt about the interpretation of the allergen-challenge findings. Also unknown is whether or not the inhibition of mast-cell mediator release occurs in parallel to an inhibition of cytokine release and thus cell recruitment. There is conflicting evidence for cetirizine. For example, cetirizine appears not to affect eosinophil recruitment in the nasal allergen challenge model (40) but does have such an effect in some other challenge models, such as skin blister (44). Lavage studies also have produced contradictory findings (45, 46). In our own studies in naturally occurring seasonal rhinitis, cetirizine failed to show a clear anti-inflammatory effect, at least as indicated by tissue eosinophil accumulation (47). Cetirizine, however, has been found to reduce nasal epithelial ICAM-1 expression in naturally occurring disease (48).

Moreover, if cetirizine does prevent eosinophil accumulation, greater clinical benefit would be expected with prophylactic than with short-term use, but this does not appear to be the case. The effect of active prophylactic therapy of H_1-antihistamines on nasal congestion is also not significantly superior to that of placebo (49), in contrast to that with corticosteroids. A study of prophylactic flunisolide and beclomethasone in patients with ragweed-sensitive rhinitis found that both prevented the development of seasonal rhinitis (50).

Comparative and combination clinical studies

In clinical comparisons, corticosteroids are significantly more effective than H_1-antihistamines (51). The *in vitro* findings with the two classes of compounds suggest a complementary mechanism of action: i.e., that there is a potential for inhibition both of mast-cell and basophil degranulation and of cell activation and eosinophil recruitment. If corticosteroids and antihistamines were used concomitantly, this might be translated into additional clinical benefit. The limited studies available, however, do not support a superior effect with long-term regular therapy with the

combination compared with topical corticosteroid alone (52, 53).

Conclusions

The broad effect of topical corticosteroid therapy in reducing the mucosal accumulation of the major effector cells of the disease, mast cells and eosinophils, accounts for their substantial clinical benefit. The lack of additional clinical benefit when antihistamines are used in combination with corticosteroids indicates that, *in vivo*, the anti-inflammatory effects on the airway of corticosteroids overlap those of the H_1-antihistamines, making the action of the latter redundant. An alternative explanation is that the *in vitro* effects of antihistamines are not evident *in vivo*, possibly due to inadequate potency at the dose used.

Thus, first-line therapy for rhinitis based on anti-inflammatory activity is a topical corticosteroid such as fluticasone propionate. A better understanding of those properties of H_1-antihistamine molecules that are relevant to cell activation and accumulation may allow the development of other molecules with appropriate potency at standard oral doses. This would extend the profile of antihistamines beyond their inhibition of the end-organ effects of histamine.

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REVIEW ARTICLE

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Intranasal Corticosteroids for Allergic Rhinitis

Superior Relief?

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Contents

Abstract

Whether first-line pharmacological treatment of allergic rhinitis should be antihistamines or intranasal corticosteroids has been discussed for several years.

First-generation antihistamines are rarely used in the treatment of allergic rhinitis, mainly because of sedative and anticholinergic adverse effects. On the basis of clinical evidence of efficacy, no second-generation antihistamine seems preferable to another. Similarly, comparisons of topical and oral antihistamines

have been unable to demonstrate superior efficacy for one method of administration over the other.

Current data documents no striking differences in efficacy and safety parameters between intranasal corticosteroids.

When the efficacy of antihistamines and intranasal corticosteroids are compared in patients with allergic rhinitis, present data favours intranasal corticosteroids. Interestingly, data do not show antihistamines as superior for the treatment of conjunctivitis. Safety data from comparative studies in patients with allergic rhinitis do not indicate differences between antihistamines and intranasal corticosteroids. Combining antihistamines and intranasal corticosteroids in the treatment of allergic rhinitis does not provide any additional effect to intranasal corticosteroids alone. On the basis of current data, intranasal corticosteroids seem to offer superior relief in allergic rhinitis than antihistamines.

Allergic rhinitis is a common condition elicited by an immunoglobulin (Ig)E-mediated allergic inflammation of the nasal mucosa and characterised by nasal obstruction, rhinorrhoea, sneezing and nasal itch, and often accompanied by conjunctivitis. It is present in 10 to 20% of the population in industrialised countries.[1] Moreover, this prevalence seems to be increasing.[2,3] Although allergic rhinitis is not a life-threatening disease, it can severely impact on quality of life[4-6] and be associated with comorbidity from other diseases, for example, asthma and conjunctivitis.[7]

Treatment of allergic rhinitis consists of allergen avoidance, allergen-specific immunotherapy and pharmacological intervention, of which the former two lie beyond the scope of the present review. Two mainstream options have evolved for pharmacological treatment, antihistamines and topical corticosteroids. The choice between these options has been extensively discussed since the introduction of intranasal corticosteroid treatment.[8]

This review considers first-line pharmacological treatment of allergic rhinitis and will deal only with antihistamines and intranasal corticosteroids (INCS), as we consider cromones, anticholinergics, leukotriene modifiers, decongestants and systemic corticosteroids as secondary treatment options in allergic rhinitis.

Only data obtained in patients with allergic rhinitis have been considered for the comparative evidence presented in this review.

1. Antihistamines

1.1 General Considerations

Histamine is the major pathophysiological mediator of allergic rhinitis. Its role is almost exclusively mediated through the histamine H_1-receptor, whereas the role of other histamine receptors in allergic rhinitis remains to be clarified. Thus, in the context of allergic rhinitis, antihistamines are H_1-receptor antagonists.[9,10] In addition to H_1-receptor blockade, an anti-inflammatory effect of antihistamines has been proposed, as some of the newer compounds have been shown to influence cytokine production, mediator release and inflammatory cell flux.[11-19] However, other studies have been unable to confirm these findings.[20-23] Whether antihistamines offer a clinically beneficial anti-inflammatory effect in addition to inhibition of histamine remains a question to be answered.

1.2 Oral Antihistamines

Numerous H_1-receptor antagonists have been developed. For oral use, these can be divided into older first-generation [e.g. chlorphenamine (chlorpheniramine), diphenhydramine, promethazine and triprolidine] and newer second-generation antihistamines (acrivastine, astemizole, cetirizine, ebastine, fexofenadine, loratadine, mizolastine and terfenadine). This review deals with the newer antihistamines as the use of the older drugs in allergic

rhinitis is limited by their adverse effects, mainly sedation and anticholinergic activity.

All of the newer antihistamines are effective in the treatment of allergic rhinitis by decreasing nasal itching, sneezing and rhinorrhoea, but they are less effective for nasal congestion.[24-31] They are also effective for conjunctivitis and recent results seem to indicate some influence on lower airway symptoms.[32,33]

Moreover, the pharmacokinetic profile of second-generation antihistamines are advantageous when compared with the first-generation agents.[34] They have an onset of action of 1 to 2 hours which lasts for 12 to 24 hours, except for acrivastine, which has to be administered at 8-hourly intervals. With the exception of cetirizine and fexofenadine, which are excreted almost unchanged, the remaining drugs in this group are metabolised via the hepatic cytochrome P450 (CYP) system by CYP3A. As a number of other compounds, that is, antimycotic azoles, macrolide antibiotics and grapefruit juice, are also substrates for this enzyme, this obviously provides a risk for interactions.[35] This is probably a contributive factor to the occurrence of severe cardiac arrhythmias, for example, 'torsade de pointes', and fatalities, which have been described following treatment with terfenadine and astemizole.[36-38] These effects seem to be enabled through a quinidine-like action, causing a prolongation of the QT interval.[39,40] At present, no clinical evidence has demonstrated cardiac adverse effects with other second-generation antihistamines when they are used at therapeutically appropriate levels. However, it is recommended to avoid antihistamines which are CYP450 metabolised or which possess quinidine-like actions in risk groups, that is, patients with impaired hepatic function or cardiac arrhythmia.[41]

Astemizole can also act as an appetite stimulant and result in increased bodyweight.[42,43] The cause for this action remains obscure, although a central nervous system (CNS)-mediated mechanism, for example, serotonin (5-hydroxytryptamine)-antagonism, is a theoretical possibility. However, whether this adverse effect is seen exclusively with astemizole remains unknown as there is a lack of data on the other second-generation antihistamines for this measure.

Whereas CNS-related adverse effects were a major characteristic of the first-generation antihistamines, the piperazine/piperidine-derived structures of the newer generation agents reduce CNS penetration, although sedative effects have been described for some of the compounds, for example, acrivastine[44] and cetirizine.[45] The binding affinity to muscarinic receptors is also decreased with the second-generation agents. With the exception of the cardiac adverse effects, this provides a more acceptable therapeutic index for the second-generation antihistamines.

1.3 Topical Antihistamines

Two newer H_1-receptor antagonists are available for topical use, azelastine and levocabastine. When applied intranasally, they have both proven effective in the treatment of allergic rhinitis, mainly relieving nasal itching and sneezing.[46,47] They have a faster onset of action than oral antihistamines and act within 15 to 30 minutes. They only need to be applied twice daily.

No sedative effects have been seen with either drug,[46,48] whereas the occurrence of a short lasting perversion of taste has been described for azelastine.[49]

1.4 Comparative Effect of Antihistamines

1.4.1 Single Dose Studies

Many studies have been performed to compare the effects of oral second-generation antihistamines in the treatment of allergic rhinitis. Single dose studies in patients with allergic rhinitis have demonstrated that cetirizine and terfenadine have a faster onset of action than loratadine and astemizole.[50,51] All 4 drugs were equally effective against nasal symptoms and histamine-induced increases in nasal airway resistance. This contrasts somewhat with the results of 2 studies in which cetirizine was superior to loratadine after administration of a single dose in both symptom relief[52] and response to histamine challenge.[53] One study

was able to demonstrate a significantly faster onset of action for fexofenadine compared with terfenadine in relief of rhinorrhoea and sneezing immediately after nasal allergen challenge.[54] This may be explained on the basis of fexofenadine being the active metabolite of terfenadine.

1.4.2 Perennial Allergic Rhinitis

Relatively few studies investigating continuous administration of antihistamines are in patients with perennial allergic rhinitis (PAR). Six studies ranging from 1 to 8 weeks, included comparisons of astemizole[55,56] cetirizine,[56-58] ebastine,[57] loratadine,[55,59,60] mizolastine[59] and terfenadine.[58,60] No differences between agents were seen except that astemizole was more effective than loratadine for rhinorrhoea in 1 short-term study,[55] and cetirizine was better than ebastine according to the investigators opinion in another study.[57] Interestingly, in 1 of the studies, nonresponders were crossed to the opposite drug at the end of a 2 week treatment period, resulting in an effect in 11 of the 16 patients.[60]

1.4.3 Seasonal Allergic Rhinitis

The lack of difference in effectiveness between second-generation drugs is also found in patients with seasonal allergic rhinitis (SAR). One placebo-controlled study in 202 patients with SAR seems to designate cetirizine as superior to loratadine,[61] as seen in the single-dose study,[51] when all symptoms following allergen challenge were considered. However, this effectiveness in symptom relief after a quite short treatment period of 2 days could not be confirmed in another placebo-controlled, cross-over study of identical treatments given for 1 week.[62]

Several seasonal studies involving acrivastine,[63] astemizole[42,64] cetirizine,[64-69] ebastine,[67] fexofenadine,[68] loratadine,[42,70] mizolastine[69] and terfenadine[65,66,70] have been unable to demonstrate any difference in efficacy for symptom relief. Some studies demonstrate small differences, that is, 'subjective rating' of cetirizine over astemizole[71] or investigator preference of ebastine over cetirizine[72] without any support for this in other endpoints, for example, symptom relief. One study shows cetirizine to have a faster onset of action than terfenadine,[73] while another claims ebastine to achieve maximum effect faster than cetirizine.[72] The use of other objective endpoints such as nasal peak flow[70] and inflammatory mediators in nasal lavage fluid[74] has not shown differences between agents.

1.4.4 Studies in Children

Data on the efficacy in children with allergic rhinitis are sparse. One single-blind study in children with SAR for 2 weeks showed equal effect of loratadine and astemizole.[75] In another 4-week study in children with PAR, cetirizine was superior to loratadine according to parental assessment.[76]

1.4.5 Topical vs Oral Antihistamines

In comparisons between oral and topical antihistamines, most topical regimens have included intranasal as well as ocular medications or reports have only addressed nasal symptoms. In 1 study, intranasal azelastine was more effective than cetirizine at relieving nasal congestion,[77] whereas other studies have demonstrated azelastine to be equally effective as cetirizine,[78] ebastine,[79] loratadine[80] and terfenadine.[81] In 2 studies, intranasal levocabastine has been marginally more effective than terfenadine in relieving single symptoms, ie. sneezing[82] and nasal itching,[83] whereas a third study did not show any difference.[84] In 1 study,[83] levocabastine given as eye drops were also judged superior to terfenadine for relieving ocular symptoms. A comparison of levocabastine and loratadine showed identical efficacy.[85]

1.4.6 Safety

When considering adverse effects, only 2 of the previously mentioned studies indicate differences. A large, placebo-controlled, 2-week study in 821 patients with SAR showed a significantly higher degree of sedation after cetirizine than fexofenadine.[68]

In another smaller 8-week study in 27 patients with SAR, terfenadine revealed more adverse effects, that is, headache and dizziness, than a combination of intranasal and ocular levocabastine.[82]

2. Corticosteroids

2.1 General Considerations

Allergic rhinitis is an inflammatory disease of the nasal mucosa and corticosteroids are, at present, the most potent anti-inflammatory medications commercially available for the treatment of allergic rhinitis.[86] Corticosteroids exert their effect by combining with a glucocorticoid receptor localised in target cell cytoplasm. The resulting activated glucocorticoid receptor complex is able to interact with cellular DNA, thereby enabling regulation of cellular functions.[87,88]

Corticosteroids act upon many of the cell types and inflammatory mediators participating in allergic inflammation. Antigen-presenting Langerhans' cells are reduced in number by INCS.[89,90] Moreover, such treatment seems to impair their processing of antigen.[91] Similarly, the migration of basophils and mast cells to the nasal epithelium is inhibited by INCS.[91-94] Evidence suggesting an impact on the release of mast cell mediators, that is, histamine, has also been presented.[95] Corticosteroid therapy interferes with several pivotal aspects of eosinophil function. Cell survival is decreased and the ability to release preformed cytotoxic proteins, that is, eosinophil cationic protein and eosinophil peroxidase, is inhibited.[96,97] Moreover, formation of a number of cytokines and chemokines vital to eosinophil lifespan are inhibited, for example, interleukin (IL)-5 (formation),[98] IL-4 (adhesion)[99] and RANTES [Regulated on Activation, Normal T cell Expressed and Secreted] (chemotaxis).[100] Results demonstrating an inhibitory effect of intranasal corticosteroid on activated T cells in nasal epithelium have been presented.[101] In 2 studies, the allergen-induced increase of specific IgE in patients with PAR during season was abolished.[102,103] In all, this indicates profound effects of corticosteroids on the inflammatory process seen in allergic rhinitis.

2.2 Intranasal Corticosteroids

Since the introduction of beclomethasone,[8] several corticosteroids have been developed for intranasal application, all characterised by a high receptor affinity and an extensive first-pass metabolism in the liver. Effectiveness in relieving the symptoms of allergic rhinitis, including nasal congestion, have been demonstrated for beclomethasone,[104] budesonide,[105] flunisolide,[106] fluticasone propionate,[107] mometasone[108] and triamcinolone.[109] In addition, some reports have indicated that INCS may have a beneficial effect towards bronchial hyperresponsiveness and asthma symptoms.[110-115]

It has been generally considered that INCS have a slow onset of action. However, they usually act within 12 to 24 hours.[116-118] Recent results have even indicated that budesonide acts after 3 hours.[119] However, maximum treatment efficacy occurs after days or a few weeks.[120] Once-daily application has proven sufficient to treat most patients with allergic rhinitis,[121-125] although those with severe symptoms may benefit from twice daily administration.[126]

The different potencies of INCS are important when considering comparative data. It is well established that fluticasone propionate is twice as potent as beclomethasone.[107] There is controversy regarding relative potencies between other INCS. However, it appears that the newer drugs, that is, fluticasone propionate and mometasone, are more potent than the others.[117]

Currently available INCS are generally well tolerated. Sneezing caused by nasal hyperactivity can occur at the start of therapy but this usually disappears with time.[127]

Occasionally, mild and transient dryness, crusting and blood-stained secretions occur, and these are often responsive to a reduction of INCS dose.[120,128,129] Septal perforation has been described as a rare complication.[130,131] Atrophy of the mucosa, corresponding to dermal atrophy, after prolonged use of INCS has not been observed.[132,133]

Because a proportion of intranasally applied corticosteroids end up in the gastrointestinal tract and is systemically absorbed, the risk of systemic adverse effects has been a concern for this class of drugs. However, these compounds, especially the

newer fluticasone propionate and mometasone, have low systemic bioavailability, mainly because of their massive first-pass metabolism in the liver.[117] When used exclusively intranasally at therapeutic dosages, the drugs in this class do not seem to exhibit any influence on the hypothalamus-pituitary-adrenal (HPA)-axis.[134-137] However, a lack of HPA-axis suppression does not guarantee against other systemic adverse effects. Data demonstrating an inhibitory effect on the short term growth rate of children have been presented for beclomethasone and budesonide,[138,139] although the result for budesonide was only achieved by giving an adult dose of 200μg twice daily. Moreover, this could not be reconfirmed in a recent study in which the impact on child growth, as measured by lower leg knemometry, of budesonide 400μg daily was comparable to placebo.[140] Other systemic adverse effects, which have been linked to inhaled therapy, for example, cataract, glaucoma and dermal thinning, do not seem to occur in patients receiving treatment exclusively by the intranasal route.[141]

2.3 Comparative Effect of Intranasal Corticosteroids

2.3.1 Perennial Allergic Rhinitis

As corticosteroids need continuous application to achieve maximum effect, single dose studies are, obviously, not very useful for comparing efficacy. Considering the many comparisons performed, not many have used a randomised, double-blind and eventually placebo-controlled design. Unless otherwise stated, the comparative studies discussed in this section (2.3) have used the drugs in standard recommended doses for allergic rhinitis.

Four placebo-controlled studies in patients with PAR have been published. Two studies[142,143] compared 1 dose of beclomethasone with 2 dose levels of fluticasone propionate in 183 patients for 12 weeks and in 466 patients for 26 weeks, respectively. The 2 remaining studies, each lasting 12 weeks, both considered mometasone. One was a comparison with beclomethasone at twice the standard daily dose in 387 patients[123] and the other regarded an equi-nominal dose of fluticasone propionate in 459 patients.[144] None of these studies revealed any difference in the relief of symptoms of allergic rhinitis or in the physicians assessment of treatment efficacy. Moreover, nasal cytology specimens were unable to demonstrate differences between treatments in 2 of the studies.[142,143]

One randomised, double-blind, 1-year study in 251 patients reported a significantly better effect with fluticasone propionate compared with an equi-nominal dose of beclomethasone on nasal congestion and secretion as well as relief of ocular symptoms.[145] These findings can partly be explained by the higher potency of fluticasone propionate. Of note, the difference was not reconfirmed by the 2 studies discussed in the previous paragraph.[142,143] A smaller randomised, double-blind, cross-over study comparing beclomethasone and flunisolide in 23 patients with perennial rhinitis, 15 of whom were allergic, did not show differences in efficacy for symptom relief or on more objective parameters of nasal blockage, that is, nasal peak flow and posterior rhinomanometry.[146]

In contrast, 2 studies comparing beclomethasone and budesonide with single-blind[147] or non-blind[148] design seem to favour the latter. Two single-blind studies have compared fluticasone propionate and budesonide. One study[149] demonstrated budesonide to be superior, especially for relief of nasal congestion. The other study,[128] which compared budesonide 200 and 400μg daily given by turbuhaler to fluticasone propionate 200μg daily, did not reconfirm this. One single-blind[150] and 1 non-blind study[151] have shown beclomethasone and flunisolide to be equally effective.

2.3.2 Seasonal Allergic Rhinitis

Comparisons of efficacy between INCS in patients with SAR do not differ significantly from those in patients with PAR. Two randomised, double-blind, placebo-controlled comparisons of beclomethasone and mometasone, which both included >300 patients, over a period of 4 and 8 weeks, respectively,[152,153] did not demonstrate differences between the 2 agents. Similarly, no dif-

ference in treatment effect was seen in another study of similar design, which compared beclomethasone and fluticasone propionate in 313 patients for 2 weeks.[154] Only 1 randomised, double-blind study has shown a difference between 2 INCS, that is, beclomethasone and budesonide.[155] However, this 7-week study, which included 56 patients, had variable dose administration, ranging from 0 to 800μg daily, and the difference was seen as less consumption of doses in the budesonide group.

No differences in treatment effect were seen in 1 non-blind[156] and 2 single-blind[157,158] comparisons of beclomethasone and flunisolide, even though 1 study used a rather low dose of beclomethasone.[158] Similarly, in single-blind comparisons, flunisolide was equivalent to budesonide[159] and triamcinolone was equivalent to fluticasone propionate.[160]. Budesonide was superior to beclomethasone in relief of sneezing in 1 single-blind comparison[161] and for relief of sneezing, nasal secretion and itching in another.[162] In a single-blind study, 2 dose levels of budesonide were compared with 1 dose level of fluticasone propionate.[163] This showed a marginally better effect of the higher dose of budesonide on sneezing but otherwise no differences between the 2 drugs.

2.3.3 Safety

The occurrence of adverse effects was similar in all of the comparisons of INCS discussed in this section (2.3), apart from 2 studies showing less nasal irritation with budesonide than flunisolide and beclomethasone, respectively.[155,159] Only 3 studies have compared the systemic impact of INCS in patients with allergic rhinitis. Two of these have been mentioned already, one comparing budesonide and fluticasone propionate in adults[128] and the other budesonide and mometasone in children.[140] The first was unable to disclose differences in urine cortisol levels, while the second did not reveal any differences in short term leg growth rate. The third study considered the influence of budesonide, mometasone and triamcinolone on plasma and urine cortisol levels as well as serum osteocalcin levels and blood eosinophil counts.[137] It applied a single-blind, cross-over, placebo-controlled design with treatment periods of five days in 20 patients with allergic rhinitis. No differences between treatments were seen for any of the parameters.

3. Comparing Antihistamines and Intranasal Corticosteroids

3.1 Perennial Allergic Rhinitis

A number of studies have compared antihistamines and INCS in patients with allergic rhinitis (table I and II).

Few studies have been performed in patients with PAR. Two 4-week studies compared terfenadine to beclomethasone[164] and astemizole with budesonide,[165] respectively. Both demonstrated that the INCS was superior for the relief of nasal symptoms. One small (n = 8) 12-week study of astemizole and beclomethasone was unable to show differences between the 2 drugs.[166]

Topical antihistamines and INCS have also been compared, with no demonstrable differences shown between azelastine and beclomethasone for relief of symptoms, physicians assessment of efficacy or nasal blockage, as measured by rhinomanometry.[167] However, when azelastine was compared with budesonide, the INCS was significantly superior for all nasal symptoms.[168] A single-blind comparison of levocabastine and beclomethasone, which was a follow-up on a double-blind comparison of levocabastine and placebo, demonstrated that beclomethasone provided better relief of nasal obstruction.[169]

3.2 Seasonal Allergic Rhinitis

Several comparisons of antihistamines and INCS have been conducted in patients with SAR, almost all being randomised and double-blind studies (table I and II).

The results of 14 comparative studies of oral antihistamines, in a total of >2500 patients, have been presented (terfenadine *vs* beclomethasone[170,171] and fluticasone propionate;[20,172,173] loratadine *vs* beclomethasone,[174] triamcinolone[175,176] and fluticasone propionate;[177,178] astemizole *vs* beclometh-

Table I. Comparative studies of oral antihistamines and intranasal corticosteroids in patients with allergic rhinitis.

Reference	Study design	No. of pts	Active treatments (daily dose)	Duration (weeks)	Comparative efficacy[a]
Perennial allergic rhinitis					
Robinson et al.[164]	r,db,co	18	Terfenadine 120mg/beclomethasone 400μg	2x4	Beclomethasone > terfenadine
Bunnag et al.[165]	r,db	67	Astemizole 10mg/budesonide 400μg	4	Budesonide > astemizole
Sibbald et al.[166]	nb,co	8	Astemizole 10-30mg/beclomethasone 400μg	2x12	NS
Seasonal allergic rhinitis					
Bronsky et al.[20]	r,db	348	Terfenadine 120mg/fluticasone propionate 200μg	4	Fluticasone propionate > terfenadine
Beswick et al.[170]	r,db	49	Terfenadine 120mg/beclomethasone 400μg	4	Beclomethasone > terfenadine[b]
Lancer et al.[171]	r,db	18	Terfenadine 120mg/beclomethasone 400μg	8	NS
Darnell et al.[172]	r,db,p	214	Terfenadine 120mg/fluticasone propionate 200μg	6	Fluticasone propionate > terfenadine
van Bavel et al.[173]	r,db,p	232	Terfenadine 120mg/fluticasone propionate 200μg	2	Fluticasone propionate > terfenadine
Frolund[174]	r,db	60	Loratadine 10mg/beclomethasone 400μg	3	Beclomethasone > loratadine
Condemi et al.[175]	r,db	348	Loratadine 10mg/triamcinolone 220μg	4	Triamcinolone > loratadine
Schoenwetter and Lim[176]	r,db	274	Loratadine 10mg/triamcinolone 220μg	4	Triamcinolone > loratadine
Gehanno and Desfougeres[177]	r,db	114	Loratadine 10mg/fluticasone propionate 200μg	4	Fluticasone propionate > loratadine
Jordana et al.[178]	r,db	240[c]	Loratadine 10mg/fluticasone propionate 200μg	4	Fluticasone propionate > loratadine
Salomonsson et al.[179]	r,db	158	Astemizole 10mg/beclomethasone 400μg	5	Beclomethasone > astemizole
Wood[180]	r,db	74	Astemizole 10mg/beclomethasone 400μg	~15	NS
Bernstein et al.[181]	r,db	209	Astemizole 10mg/triamcinolone 220μg	4	Triamcinolone > astemizole
Vervloet et al.[182]	r,db	238	Cetirizine 10mg/fluticasone propionate 200μg	3	Fluticasone propionate > cetirizine

a Statistically significant difference between active medications for one or more nasal symptoms.

b During high exposure.

c Adolescents.

co = cross-over; **db** = double-blind; **nb** = nonblind; **NS** = no significance; **p** = placebo-controlled; **r** = randomized; > indicates significantly better than.

asone[179,180] and triamcinolone;[181] and cetirizine *vs* fluticasone propionate.[182] With the exception of 2 studies,[171,180] all demonstrated the INCS to be more effective in the relief of nasal symptoms than the oral antihistamine.

Of the exceptions, 1 study, which compared astemizole to beclomethasone in 74 patients, demonstrated similar effects on nasal symptoms.[180] A possible explanation could be that a very long study period of approximately 15 weeks for the grass pollen season was used, thereby imposing a risk of diluting differences depending on pollen exposure. In fact, the paper lacks pollen data for the last 17 days of the study period. Although the sec-

ond study did not demonstrate differences between the agents in symptoms, it showed the INCS to have a superior effect on an objective measure of nasal obstruction, that is, rhinomanometry.[171]

This difference in nasal obstruction measured objectively was also seen in 1 of the studies demonstrating a difference between an antihistamine and INCS in nasal symptomatology.[20]

In the 1 study in adolescents, fluticasone propionate was more effective than loratadine in the relief of nasal peak inspiratory flow rate in a subgroup of patients.[178] Two studies were able to demonstrate significant reductions in the number of nasal mucosal eosinophils only with INCS.[20,173]

Conjunctivitis is often a major problem in patients with SAR. One of the reasons for using oral antihistamines rather than INCS has been because of the anticipated better effect on ocular symptoms. However, only 2 of the studies discussed in this section have confirmed this.[174,180]

The apparent superiority of INCS to oral antihistamines on relief of nasal symptoms was confirmed by a recent meta-analysis of 16 studies involving 2267 subjects,[183] which demonstrated that INCS were more effective in relief of nasal obstruction, secretion, itching and sneezing as well as total nasal symptom score. Moreover, the meta-analysis was unable to demonstrate any difference between the 2 drug classes on ocular symptoms.

Data on the comparative efficacy of topical antihistamines and INCS in patients with SAR are also available (table II). Azelastine has been compared with beclomethasone in 2 studies, one of which showed beclomethasone as more effective in relieving nasal symptoms,[184] and the other revealed fewer eosinophils in nasal lavage but no difference on nasal symptoms.[185] Two small nonblind studies comparing azelastine to budesonide were unable to discriminate between treatments.[186,187] Three studies involving levocabastine have been reported, 1 compared this agent with budesonide[188] and 2 with fluticasone propionate.[189,190] All 3 studies demonstrated the INCS was superior in the relief of nasal symptoms. Moreover, fluticasone propionate reduced the number of eosinophils in nasal lavage fluid in both studies,[189,190] as well as

Table II. Comparative studies of topical antihistamines and intranasal corticosteroids in patients with allergic rhinitis.

Reference	Study design	No. of pts	Active treatments (daily dose)	Duration (weeks)	Comparative efficacy[a]
Perennial allergic rhinitis					
Davies et al.[167]	r,db,p	130	Azelastine 560μg/beclomethasone 400μg	6	NS
Stern et al.[168]	r,db,p	195	Azelastine 560μg/budesonide 256μg	6	Budesonide > azelastine
van de Heyning et al.[169]	r,sb	21	Levocabastine 800μg/beclomethasone 400μg	2[b]	Beclomethasone > levocabatine
Seasonal allergic rhinitis					
Newson-Smith et al.[184]	r,db,p	243	Azelastine 1120μg/beclomethasone 400μg	2	Beclomethasone > azelastine
Pelucchi et al.[185]	r,db,p	36	Azelastine 560μg/beclomethasone 200μg	6	NS
Dorow et al.[186]	r,nb	36	Azelastine 560μg/budesonide 200μg	2	NS
Wang et al.[187]	r,nb	14	Azelastine 1120μg/budesonide 400μg	2	NS
Svensson et al.[188]	r,sb,p	44	Levocabastine 400μg/budesonide 400μg	5	Budesonide > levocabastine
Di Lorenzo et al.[189]	r,db,p	24	Levocabastine 400μg/fluticasone propionate 200μg	6	Fluticasone propionate > loratadine
Ortolani et al.[190]	r,db,p	288	Levocabastine 400μg/fluticasone propionate 200μg	6	Fluticasone propionate > levocabastine

a Statistically significant difference between active medications for one or more nasal symptoms.

b Follow-up of double-blind comparison between levocabastine and placebo.

db = double-blind; **nb** = nonblind; **NS** = no significance; **p** = placebo-controlled; **r** = randomized; **sb** = single-blind; > indicates significantly better than.

Table III. Comparative studies on combinations of oral antihistamines and intranasal corticosteroids in patients with seasonal allergic rhinitis.

Reference	Study design	No. of pts	Active treatments (daily dose)	Duration (weeks)	Comparative efficacy[a]
Juniper et al.[191]	r,db	90	Astemizole 10mg, beclomethasone 400µg, astemizole 10mg + beclomethasone 400µ	6	Astemizole + beclomethasone = beclomethasone > astemizole
Ratner et al.[192]	r,db,p	600	Loratadine 10mg, fluticasone propionate 200µg, loratadine 10mg + fluticasone propionate 200µg	2	Loratadine + fluticasone propionate = fluticasone propionate > loratadine
Simpson[193]	r,db,p	106	Terfenadine 120mg, budesonide 400µg, terfenadine 120mg + budesonide 400µg	3	Terfenadine + budesonide = budesonide> terfenadine
Brooks et al.[194]	r,db	60	Loratadine 10mg, beclomethasone 336µg, loratadine + beclomethasone 336µg	2	Loratadine + beclomethasone > beclomethasone = loratadine
Backhouse et al.[195]	r,sb	99	Terfenadine 120mg, terfenadine 120mg + flunisolide 200µg	11	Terfenadine + flunisolide > terfenadine
Juniper et al.[196]	r,nb	61	Terfenadine 60-120mg (+fluticasone propionate prn) fluticasone propionate 200-400µg (+Terfenadine prn)	6	NS[b]

a Statistically significant difference between active medications for one or more nasal symptoms.

b Only expressed as quality of life.

db = double-blind; **nb** = nonblind; **NS** = no significance; **p** = placebo-controlled; **prn** = as required; **r** = randomized; **sb** = single-blind; = indicates equal to; > indicates significantly better than.

eosinophil and mast cell markers of nasal lavage in 1 study.[189]

3.3 Combination of Antihistamines and Intranasal Corticosteroids

A combination of an antihistamine and INCS is often used in clinical practice. Four studies have included a treatment arm of such combination therapy in addition to treatment arms of antihistamine and INCS monotherapy (table III). Three of these, including almost 800 patients, showed that the combination therapy, although better than antihistamine alone for relief of nasal symptoms, offered no advantages over INCS alone.[191-193] The fourth study in 60 patients demonstrated the combination of loratadine and beclomethasone as significantly superior to beclomethasone alone for the outcomes of sneezing and nasal itching.[194]

One study has compared the combination of terfenadine and flunisolide to terfenadine alone and demonstrated a better effect of the combination for relief of nasal symptoms and in the investigator assessment of treatment.[195] Another study with a nonblind design, which assessed terfenadine and fluticasone propionate offering the opposite drug on an as needed basis, was unable to demonstrate any difference in quality of life measures.[196] This parameter was also applied in 2 other studies, where the INCS-containing treatments produced a better quality of life.[175,192]

3.4 Safety

In contrast to the differences demonstrated for efficacy between antihistamines and INCS in all these comparative studies, no quantitative differences were observed regarding occurence of adverse effects. Minor qualitative differences can be observed, eg. nasal crusting for INCS and sedation for antihistamines. However, in general, occurence of adverse effects is low in both treatments. This includes results of morning plasma cortisol levels, albeit not an ideal indicator of HPA-axis interference, which were performed in three studies.[20,173,190]

3.5 Cost Effectiveness

The cost effectiveness of treatments is naturally dependent on local prizes for the respective medications. However, two cost analyses seem to favour INCS over oral antihistamines. In the US, fluticasone propionate was more cost effective than terfenadine, when medications were needed for more than 11 to 22 days,[197] when comparing direct costs of medication to effect upon nasal symptoms and patient overall assessment. In Canada fluticasone propionate was 2.5 and 5.7 times as cost effective, respectively, than terfenadine and loratadine, when comparing direct costs of medication to days without nasal blockage.[198]

The combination use of oral antihistamines and INCS, which appears to offer no or a marginal clinical benefit compared with the use of INCS alone, cannot be considered to be cost effective.

4. Conclusion

A recent review[199] was unable to conclude any differences of efficacy between oral second-generation antihistamines, when considering the results of the relatively few existing randomised, double-blind, placebo-controlled studies of patients with SAR. This view is largely supported by data from randomised, double-blind comparator studies over the last decade for both SAR and PAR. Moreover, no differences have been documented by comparisons of systemic and topical second-generation antihistamines, when the latter were given both via the nose and the eyes.

No striking differences in efficacy in patients with allergic rhinitis have been demonstrated in comparisons of INCS at recommended doses. Similarly, existing clinical evidence on adverse effects do not convincingly support the theoretically-based superiority of newer compounds, for example, fluticasone propionate and mometasone. On the other hand, beclomethasone and budesonide provide the greatest amount of experience accumulated during more than 20 years. *In summary*, the available clinical evidence does not support one drug among the available INCS as superior.

The currently available comparative data on the efficacy of INCS and antihistamines clearly support INCS as more effective in the relief of nasal symptoms in patients with allergic rhinitis. Moreover, this is substantiated by results for other study endpoints, that is, inflammatory parameters, acoustic rhinometry, rhinomanometry and quality of life assessments. Interestingly, present evidence does not support a difference between these 2 drug classes in effective control of ocular symptoms. No quantitative differences have been demonstrated between INCS and antihistamines regarding occurence of adverse effects in safety data. The common clinical practice of combining INCS and oral antihistamines in the treatment of allergic rhinitis has no support in clinical evidence, as the combination has not provided effects beyond INCS alone and so it cannot be considered cost effective.

International consensus reports[41,200] recommend INCS as first-line treatment in SAR and in PAR (adults) for patients with moderate to severe disease with regular or daily symptoms. Antihistamines are recommended as first-line treatment in patients with mild disease with infrequent symptoms, and in children with PAR.

This review supports the notion that INCS offer superior relief for the symptoms of allergic rhinitis. As long term experience has shown the treatment to be very well tolerated, INCS have a high therapeutic index and can be recommended as an effective treatment for allergic rhinitis.

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REVIEW ARTICLE

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Safety and Tolerability Profiles of Intranasal Antihistamines and Intranasal Corticosteroids in the Treatment of Allergic Rhinitis

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Contents

Abstract

Intranasal corticosteroids and intranasal antihistamines are efficacious topical therapies in the treatment of allergic rhinitis. This review addresses their relative roles in the management of this disease, focusing on their safety and tolerability profiles. The intranasal route of administration delivers drug directly to the target organ, thereby minimising the potential for the systemic adverse effects that may be evident with oral therapy. Furthermore, the topical route of delivery enables the use of lower doses of medication. Such therapies, predominantly available as aqueous formulations following the ban of chlorofluorocarbon propellants, have minimal local adverse effects.

Intranasal application of therapy can induce sneezing in the hyper-reactive nose, and transient local irritation has been described with certain formulations. Intranasal administration of corticosteroids is associated with minor nose bleeding in a small proportion of recipients. This effect has been attributed to the vasoconstrictor activity of the corticosteroid molecules, and is considered to account for the very rare occurrence of nasal septal perforation. Nasal biopsy studies do not show any detrimental structural effects within the nasal mucosa with long-term administration of intranasal corticosteroids. Much attention has focused on the systemic safety of intranasal application. When administered at standard recommended therapeutic dosage, the intranasal antihistamines do not cause significant sedation or impairment of psychomotor function, effects that would be evident when these agents are administered orally at a therapeutically relevant dosage.

The systemic bioavailability of intranasal corticosteroids varies from <1% to up to 40–50% and influences the risk of systemic adverse effects. Because the dose delivered topically is small, this is not a major consideration, and extensive studies have not identified significant effects on the hypothalamic-pituitary--adrenal axis with continued treatment. A small effect on growth has been reported in one study in children receiving a standard dosage over 1 year, however. This has not been found in prospective studies with the intranasal corticosteroids that have low systemic bioavailability and therefore the judicious choice of intranasal formulation, particularly if there is concurrent corticosteroid inhalation for asthma, is prudent. There is no evidence that such considerations are relevant to shorter-term use, such as in intermittent or seasonal disease.

Intranasal therapy, which represents a major mode of drug delivery in allergic rhinitis, thus has a very favourable benefit/risk ratio and is the preferred route of administration for corticosteroids in the treatment of this disease, as well as an important option for antihistaminic therapy, particularly if rapid symptom relief is required.

Allergic rhinitis arises following an initial sensitisation phase, in which allergen presentation results in antibody (IgE) formation and the development of atopy. Subsequently, depending upon the level of exposure and the degree of sensitisation, allergen can then trigger a humoral response, which underlies the clinical disease phase and is manifested by symptoms such as nasal itching, sneezing, rhinorrhoea and nasal obstruction. Allergic rhinitis is a common condition, having increased substantially in prevalence during the 20th century,[1] and now represents a global health problem affecting 10–25% of the world population.[2,3] The socioeconomic impact of allergic rhinitis is considerable, particularly when not only the direct costs of management but also the indirect costs from reduced productivity and absenteeism from work are taken into account. These costs do not include the further expense of treating conditions associated with allergic rhinitis, such as asthma, sinusitis, otitis media, nasal polyposis, lower respiratory tract infection and dental malocclusion.[4]

Previously, based on the timing of exposure, allergic rhinitis was subdivided into seasonal and perennial varieties. Although such a subdivision is relevant in countries such as UK, this is not so in many parts of the world where, because of the nature of the climate, typical seasonal allergens are in fact perennial. It is also recognised that in those patients who are multisensitised to allergens, such as tree, grass and weed pollens, their 'seasonal' disease is prolonged. In the recent document on allergic rhinitis and its impact on asthma (ARIA),[5] the consensus was that this classification was no longer adequate, and therefore a major change was proposed. The new classification based on the ARIA guidelines (table I) subdivides allergic rhinitis, in relation to the duration of the disease, into 'intermittent' or 'persistent' disease. The severity of allergic rhinitis is also classified as 'mild' or 'moderate-severe'.

Intranasal antihistamines and intranasal corticosteroids represent major therapeutic options as first-line medications in the management of allergic rhinitis because of the prominent role of histamine as a mediator of rhinitis and the underlying nature of the allergen-induced airway inflammation, which is glucocorticoid-responsive. Furthermore, topical intranasal therapy allows site-directed treatment with a reduced risk of systemic effects because of the low bioavailability of intranasal antihistamines and intranasal corticosteroids from this site. In blocking the end-organ effects of histamine intranasal antihistamines have a rapid onset of effect and can be used as both 'as required' therapy for intermittent disease relief and as regular daily therapy in persistent disease. In general, the clinical profile of therapeutic benefit with intranasal corticosteroids is greater than with intranasal antihistamines in rhinitis, because of the more widespread effect of intranasal corticosteroids on mucosal inflammation. Since there is a delay before the anti-inflammatory effect is clinically manifested following initiation of therapy, intranasal corticosteroids have, until recently, been predominantly used for the treatment of persistent disease. The debate is still ongoing, however, concerning the safety and tolerability profiles of intranasal antihistamines and intranasal corticosteroids, particularly in relation to the systemic bioavailability of intranasal corticosteroids and their potential to modify growth in children.

This review adopts an evidence-based approach to conduct a thorough critical and comparative analysis of the currently available data, particularly concerning the safety and tolerability profiles of intranasal antihistamines and intranasal corticoster-

Table I. Classification of allergic rhinitis according to ARIA guidelines

Allergic rhinitis	Parameters
Intermittent	Symptoms are present for <4 days per week or for <4 weeks
Persistent	Symptoms are present for >4 days per week and for >4 weeks
Mild	None of the following items are present: sleep disturbance; impairment of daily activities, leisure and/or sport; impairment of school or work; troublesome symptoms
Moderate-severe	One or more of the following items are present: impairment of daily activities, leisure and/or sport; impairment of school or work; troublesome symptoms

ARIA = allergic rhinitis and its impact on asthma.

oids, in the context of their use as topical therapeutic agents in allergic rhinitis.

A computerised literature search of Medline (1966 onwards) and Embase databases was performed using the following search terms: allergic rhinitis, seasonal, perennial, corticosteroids, antihistamines, intranasal or topical, safety, tolerability. In addition, abstracts from key meetings have been included in the search process.

It should be noted, however, that this review is neither meant to be exhaustive, nor is it intended as a systematic review or meta-analysis. Rather it aims to present a balanced perspective, based on the available evidence in the published literature, on the safety and tolerability profiles of intranasal antihistamines and intranasal corticosteroids in the treatment of allergic rhinitis.

1. Intranasal Antihistamines: Historical Perspective

Histamine H_1 receptor antagonists have been the mainstay of therapy for allergic rhinitis since they were first introduced, following the demonstration by Staub and Bovet in 1937 that this class of compounds, newly developed at that time, offers protection against allergen-induced anaphylaxis.[6] Although observational studies reported symptomatic relief in allergic rhinoconjunctivitis with the earliest antihistamines, adverse pharmacological effects, such as sedation, dry mouth, and blurred vision, limited their widespread acceptance. In addition, there was concern that asthma, often associated with rhinitis, could be worsened by antihistaminic therapy,[7,8] although this view is no longer held, nor indeed is it supported by the available evidence.

In general, an ethylamine chain is common to all H_1 receptor antagonists. Many of the additional properties of this class of compounds, with the exception of sedation, can be linked to side-chain radical structure. Structural engineering of these molecules later enabled the synthesis of H_1 receptor antagonists without the anticholinergic,[9] antiserotoninergic,[10] α-adrenergic receptor antagonistic,[11] or local anaesthetic[12] effects evident in earlier compounds. The major breakthrough in the development of H_1 receptor antagonists for clinical use came with the synthesis of the antihistamine, terfenadine, which, while retaining peripheral H_1 receptor antagonist activity, did not appear to cross the blood-brain barrier and was thus devoid of unwanted CNS antihistaminic effects, such as sedation and impairment of psychomotor function.[13] Furthermore, it had no H_2 receptor antagonism, α- or β-adrenergic receptor antagonism, antiserotoninergic or antimuscarinic effects.[14] Thus, in 1981, terfenadine was introduced as the first oral non-sedating antihistamine for the treatment of rhinoconjunctivitis. This represented a major advance in the development of H_1 receptor antagonists for use in the treatment of rhinoconjunctivitis. Other orally administered non-sedating (second-generation) H_1 receptor antagonists were then launched in the 1980s and 1990s. Topical H_1 receptor antagonists such as levocabastine for nasal and ocular administration, azelastine for nasal administration, and more recently emedastine for ocular administration, have subsequently been developed. Topical therapy has the advantage of delivering drug effectively to the target organ while avoiding or minimising systemic adverse effects. Such therapy does have a disadvantage, however, in that if it is not systemically bioavailable, it will modify disease only at that site and not disease concurrently manifesting at other target organ sites. The choice between topical therapy and systemic therapy will thus depend upon the spectrum of disease and the efficacy to safety ratio of therapies.

2. Levocabastine

2.1 General Overview

Levocabastine has been reviewed by Noble and McTavish.[15] Levocabastine is a potent and selective H_1 receptor antagonist with no appreciable affinity *in vitro* for H_2, dopaminergic, adrenergic, serotoninergic, or cholinergic receptors. The recommended nasal dosage for levocabastine is 0.1mg into each nostril twice daily and ocular dose is 0.03mg administered into each eye twice daily.[16] The nasal efficacy of levocabastine has been demonstrated

under challenge conditions.[17,18] It has a rapid onset of action (10–15 minutes) and is effective for up to 12 hours. These findings have been confirmed in the eye using conjunctival challenge.[18,19]

Administered topically, levocabastine is most effective against nasal itching, sneezing, and rhinorrhoea. There are a number of published placebo-controlled trials in seasonal allergic rhinitis,[20,21] but the majority of studies report comparisons with active medications, such as oral H_1 receptor antagonists,[22,23] sodium cromoglycate (cromolyn sodium),[20,24] or intranasal corticosteroids.[22] One placebo-controlled study reported no effect of levocabastine on nasal obstruction in patients with seasonal allergic rhinitis due to mountain cedar, when used at a dosage of 0.2mg twice daily (1 spray into each nostril twice daily), despite clear effects on the neurally-mediated symptoms of itching, sneezing, and rhinorrhoea.[21] Regular therapy with levocabastine is reported to be more effective than a topical antihistamine/decongestant (naphazoline/antazoline) preparation[22] or topical sodium cromoglycate[20,24] in the treatment of allergic rhinoconjunctivitis. A comparative study of levocabastine (0.5 mg/mL, two sprays into each nostril four times daily) and sodium cromoglycate (20 mg/mL, two sprays into each nostril four times daily) involving 114 patients over a 2-week period, found significant symptomatic improvement in allergic rhinitis with levocabastine therapy (76% patients on levocabastine improving vs 46% on sodium cromoglycate).[25] Similar results with more symptom-free days in the levocabastine-treated patients were found in another study.[20] An open observational study comparing efficacy and the onset of action of topical levocabastine nasal spray and eye drops as well as nedocromil nasal spray and eye drops showed that >80% of patients with seasonal allergic rhinitis reported symptom relief with both medications within one hour, amounting to approximately a 50% reduction in symptom severity.[26]

While levocabastine nasal spray has been reported to be as efficacious as topical nasal corticosteroids in allergic rhinitis,[22] the comparative data currently available do not support this view. Intranasal fluticasone propionate was found to be significantly more effective than levocabastine in the treatment of seasonal allergic rhinitis.[27,28] Another study, which assessed nasal nitric oxide levels as a marker of underlying nasal inflammation, reported a significant effect with nasal corticosteroids but not with topical levocabastine.[29] Comparative studies in perennial rhinitis are limited. A preliminary 2-week study reported improvement in sneezing and rhinorrhoea with topical levocabastine compared with placebo, which could not be further improved by the addition of topical nasal beclomethasone dipropionate.[30] Nasal blockage, however, did respond to the additional therapy.

Levocabastine is available as a 0.5 mg/mL microsuspension (0.05% levocabastine hydrochloride) nasal spray and eye drops. The recommended dosage in adults and children >9 years of age is two sprays into each nostril twice daily and one drop into each eye twice daily, both of which could be increased to three to four times daily. Given the renal route of excretion, levocabastine should be used with caution in patients with renal impairment.[31] Dosage recommendations for the elderly population are not currently available. This is a reflection of the relative rarity of allergic rhinitis in this age group.

2.2 Tolerability and Safety Profile

The rationale for the use of a medication for the treatment of a condition is based on assessing the drug's potential for beneficial and adverse effects. The major advantage of the second-generation H_1 receptor antagonists, which significantly improved their benefit/risk profile, was considerably reduced or absent CNS sedative effects when used at standard clinical dosages. Not all new H_1 receptor antagonists, including levocabastine, exhibited this beneficial profile when administered orally. Thus levocabastine, on account of its remarkable potency as an H_1 receptor antagonist, was subsequently developed for topical use. Because of the small volume of delivery, only those H_1 receptor antagonists with reasonable solubility and high potency are suitable for delivery by topical route. Topical therapy minimises the potential for systemic adverse effects

while preserving the therapeutic benefits. Concern that the effect of topical therapy might be limited by rhinorrhoea has not been substantiated. When experimentally-induced rhinorrhoea with methacholine was followed by intranasal levocabastine administration and nasal lavage with saline 30 seconds following intranasal levocabastine administration, there was no evidence of reduction in the efficacy of levocabastine in inhibiting histamine-induced sneezing and rhinorrhoea.[32]

Levocabastine is absorbed following intranasal administration, with systemic bioavailability typically ranging between 60–80% after a single-dose nasal administration,[33] with peak plasma concentration (C_{max}) reached after 1–4 hours.[34,35] C_{max} values of 0.78 μg/L and 1.76 μg/L were reached 2.9 and 4.3 hours following nasal application of 0.1mg and 0.2mg single doses, respectively, in healthy volunteers.[35] Similar values were obtained following repeated administration of levocabastine.[36] In another study, administration of levocabastine nasal spray (0.2mg) to non-atopic volunteers produced a peak plasma concentration range of 1.4–2.2 μg/L.[34] Detailed pharmacokinetic-pharmacodynamic testing has indicated that the clinical benefits evident with levocabastine can be attributed to the local antihistaminic effects at the site of application.[37] Coupled with the fact that levocabastine is subject to minimal hepatic metabolism, a potential site for important drug interactions, these findings suggest theoretically that the likelihood of systemic adverse effects with nasal administration of levocabastine is extremely low. With repeated doses of intranasal levocabastine in healthy volunteers, steady-state plasma concentrations are reached within 7–10 days. The extent of drug absorption appears to be related to the method of administration of topical levocabastine. Conflicting data exist as to the impact of disease on the systemic bioavailability. While higher drug plasma concentrations have been found in healthy non-atopic controls following single dose administration, the opposite effect was noted with multiple dose administration.[34] Following nasal administration, levocabastine is primarily excreted by the kidneys, with an elimination half-life of 35–40 hours.[34] Renal dysfunction may, therefore, be associated with decreased elimination of the drug.[15,31]

The tolerability profile of levocabastine nasal spray has been extensively evaluated in clinical trials. The available data suggest that topical levocabastine is well tolerated, with an adverse effect profile comparable with that of topical sodium cromoglycate and placebo.[21,38-41] A review of the adverse events reported in 1758 patients who received levocabastine nasal spray in clinical trials identified that most common adverse events encountered were headache (4%), nasal irritation (3%), somnolence (3%) and fatigue (2%).[42] None of these occurred more frequently than would have been anticipated with placebo under similar circumstances. In a multicentre, double-blind, placebo-controlled trial evaluating the efficacy and safety of levocabastine nasal spray for seasonal allergic rhinitis, the incidence of adverse events was similar for both the treatment and placebo groups.[21] In this study, most of the adverse events were mild and linked with the disease process, with the most frequently reported being sinusitis (17% in each group), headache (17% with placebo, 14% with levocabastine), and rhinitis (8% with placebo, 2% with levocabastine).[21] This profile of adverse event reporting is similar to that in numerous other clinical trials of topical levocabastine.[23,39-41,43-47] In separate studies, the overall incidence of adverse events has been comparable for levocabastine and placebo (27% vs 31%)[42] and (30% vs 32%).[48] A double-blind parallel-group study (n = 27) comparing the safety and efficacy of topical levocabastine with that of oral terfenadine over an 8-week treatment period, found the incidence of adverse events lower, at 31%, in the levocabastine group compared with 43% in the terfenadine group.[43] Other reports suggest a comparable adverse events profile between topical levocabastine and oral terfenadine (40% versus 41%).[42] To date, there has been no evidence of any clinically significant effect of topical levocabastine on haematological or biochemical parameters. Furthermore, the type and frequency of adverse effects appear to be neither related to the number of daily applications nor increased by the concomitant use of

the eye drops and nasal spray compared with the use of either formulation separately.[42]

Drug safety and tolerability profiles are crucial determinants of therapeutic choices in the paediatric population. A study involving 53 children aged between 6 and 15 years, reported levocabastine to be well tolerated in this age group, with a similar profile of adverse events to that reported in sodium cromoglycate-treated children.[41] The satisfactory paediatric tolerability profile of topical levocabastine has also been confirmed in another study involving 32 children between the ages of 5 and 11 years, who were treated with topical levocabastine over a 20-day period.[49]

2.3 Specific Safety and Tolerability Issues

2.3.1 Local Tolerability

It is well documented that intranasal administration of certain drugs, in particular decongestants, can influence ciliary motility of the upper airways.[50] Although topical administration of levocabastine can be associated with a sense of nasal irritation,[20,38,46] there is no evidence of a clinically significant effect of the drug on ciliary beat frequency or mucociliary clearance.[51] There is no evidence that levocabastine nasal spray causes any significant taste disturbance when used in the treatment of allergic rhinitis.

2.3.2 CNS Effects

Sedation is the most common adverse effect of the first-generation antihistamines because of their capacity to cross the blood-brain barrier. The severity of adverse effect could range from subclinically impaired reaction times to clear sedation. In view of its pharmacokinetic profile, particularly its low plasma concentration following intranasal administration, levocabastine is considered unlikely to be associated with any significant sedative effects.[33] This is supported by findings in specific studies of psychomotor and cognitive function following topical administration of levocabastine.[52,53] One such study investigated potential psychomotor effects of levocabastine (eye drops and nasal spray) following single- and multiple-dose administration, and compared the findings with those of oral triprolidine.[52] Performance was assessed using validated cognitive and psychomotor tests as sensitive measures of the sedative effects of psychoactive drugs. In contrast to the significant sedative effect of triprolidine, topical administration of levocabastine eye drops and nasal spray, at concentrations levels up to 2.0 mg/mL (four times the recommended concentration), had no demonstrable effect on psychomotor function in healthy volunteers.[52] There is no evidence of any pharmacokinetic or psychomotor interactions between intranasal levocabastine and alcohol or diazepam.[42]

2.3.3 Cardiovascular Effects

In vitro and *in vivo* human and animal models have been used to assess the possible cardiovascular effects of levocabastine following oral, ocular and nasal administration. The results have not revealed any demonstrable effects of levocabastine on action potential amplitude, duration, or any other key cardiovascular parameter.[42] Human studies with topically administered levocabastine did not reveal any significant ECG changes. Several studies in healthy volunteers have reported no significant effects on QT or corrected QT (QTc) intervals following treatment with levocabastine in single or repeated doses, even when the nasal spray and eye drops were used in combination four times daily (1.2 mg/day).[38,42]

2.3.4 Drug Interactions

Topical levocabastine administration is unlikely to be associated with any clinically significant drug interactions because of its low plasma concentration and negligible hepatic metabolism. However, the theoretical potential for drug interactions, in the form of binding site displacement, does exist since levocabastine has the ability to bind to plasma proteins, particularly albumin. This risk has not been seen in practice. *In vitro* studies of potential drug interactions have so far failed to show any significant alteration of plasma protein binding of many drugs, including cimetidine and ketoconazole, in relation to the concurrent administration of levocabastine. Small increases (up to 8%) in the proportion of unbound levocabastine have been identified

with certain high protein-bound drugs, such as sulfadimidine (sulfamethazine), tolbutamide and warfarin. This is of little clinical significance for levocabastine, which has a plasma protein binding level of only 55%.[33]

2.3.5 Use in Pregnancy

Topical antihistamines, including levocabastine, have not been shown to have potential teratogenic or embryotoxic effects. Hence, therapeutic use in pregnancy is not currently specifically contraindicated.[54]

2.3.6 Other Effects

There has been no evidence of carcinogenicity or tumour progression in patients taking therapeutic doses of any antihistamine.[55]

3. Azelastine

3.1 General Overview

Azelastine has been reviewed by McNeely and Wiseman.[56] Azelastine, a phthalazinone derivative, is a second-generation H_1 receptor antagonist, but caused sedation when administered orally and thus developed for topical application to the nose.[57] Topical administration via the intranasal route confines the effect largely to the nose and reduces the likelihood of adverse effects due to systemic absorption. Azelastine is selective to H_1 receptors on standard receptor affinity testing and, consistent with this, is clinically efficacious in reducing sneezing, itching and watery rhinorrhoea. In addition to its antihistaminic effect, azelastine has been reported to display additional biological activity compatible with 'anti-allergic' or 'anti-inflammatory' properties. Studies *in vitro* have shown azelastine inhibits both mast cell and basophil activation.[58] It has been proposed that such activity may explain the reports that topical nasal therapy with azelastine reduces nasal obstruction in addition to the classical histamine-mediated neural symptoms. Azelastine, administered as a nasal spray, has been found to be more effective than oral azelastine or terfenadine in relieving nasal obstruction, while producing comparable relief of other nasal symptoms.[59] Consistent with this suggestion, in a nasal allergen challenge study, Ciprandi and colleagues found that daily treatment with topical azelastine for 1 week before challenge reduced the allergen-induced epithelial expression of intercellular adhesion molecule-1 (ICAM-1) during the early and late phase reactions, as well as reducing the late phase eosinophil and neutrophil recruitment.[60] The same group have also identified that topical azelastine reduces the epithelial expression of ICAM-1 in naturally-occurring seasonal allergic rhinitis, with a more consistent effect with regular than on demand therapy.[61] A number of other antihistamines have also been shown to modify epithelial ICAM-1 expression; however, it is unclear as to whether this represents an additional biological activity or is purely a reflection of H_1 receptor blockade. Integral to the dilemma over the *in vivo* antiallergic activity of topical azelastine is the failure of this therapy to modify cell recruitment within the nose in naturally-occurring seasonal allergic rhinitis.[62] Thus, despite a number of clinical studies showing a reduction in nasal obstruction with azelastine,[56,63,64] there exists no consensus to date regarding the mechanism, particularly as not all studies have demonstrated this beneficial effect.[65,66]

Standard dosage of topical azelastine is 0.14mg into each nostril twice daily. While in one study half the standard daily dosage (0.28 mg/day) was found to be as effective as the standard dosage (0.56 mg/day) in improving symptoms, the benefit of the standard dose was reflected by a significantly greater use of rescue medication in the lower dosage treatment group.[61] Symptomatic improvement is reported as early as 30 minutes following the intranasal administration of azelastine, in a high-dose treatment regimen (two puffs into each nostril [0.56 mg]), and is apparent for up to 12 hours in patients with seasonal allergic rhinitis.[56] There have been a number of placebo-controlled trials of azelastine in allergic rhinitis. One such trial involving a 6-week study of azelastine nasal spray (0.14mg into each nostril twice daily; total dosage 0.56mg) in children with perennial allergic rhinitis reported a beneficial effect compared with placebo on all nasal symp-

toms, including nasal obstruction.[67] The clinical efficacy of azelastine nasal spray has also been demonstrated in the treatment of vasomotor (perennial non-allergic) rhinitis.[68,69] Other studies have focused on comparisons in seasonal and perennial allergic rhinitis with other active medications, such as antihistamines[63,66] and nasal corticosteroids.[62,70-75]

While azelastine nasal spray has been reported to be as efficacious as topical nasal corticosteroids, such comparative studies are limited and further studies are required before valid comparisons can be made. One study involving seasonal allergic rhinitis patients receiving nasal corticosteroids or oral antihistamines who remained symptomatic after a 1- to 2-week washout period, compared double-dose azelastine (1.1 mg/day) with the combination of loratadine (10mg daily) and nasal beclomethasone (336 μg/day).[70] Following one week of treatment, no statistical difference was evident between the treatments, and it was concluded that azelastine was as effective as the combination therapy with loratadine and beclomethasone.[70] However, caution has to be exercised when interpreting results of such a study, as the effect of the nasal corticosteroid is unlikely to have been fully expressed within the time frame of the study. Therefore, this study essentially might have represented a basic comparison of azelastine and loratadine. Intranasal azelastine (one puff into each nostril twice daily) is generally as effective as standard therapeutic doses of other antihistamines, including intranasal levocabastine[76] and oral cetirizine,[77,78] ebastine,[79] loratadine[80] and terfenadine[81] in achieving symptomatic improvement in patients with allergic rhinitis.

Azelastine nasal spray is available as a 1 mg/mL solution of azelastine hydrochloride in a metered dose pump spray bottle (0.14 mg/metered spray). The US prescribing recommendations specify two puffs into each nostril twice daily for adults and children aged ≥12 years. In the UK and a number of other European countries, however, azelastine is recommended as one spray into each nostril twice daily for adults and children ≥5 years.[82]

3.2 Tolerability and Safety Profile

There is a paucity of peer-reviewed publications on pharmacokinetic properties of intranasal azelastine. Following 29 days of intranasal azelastine at a dosage of 0.56 mg/day, a maximum plasma concentration of 0.306 μg/L was achieved approximately 2.5 hours after administration.[59,83,84] The mean steady-state plasma concentration of intranasal azelastine was 0.26 μg/L in healthy volunteers compared with 0.65 μg/L in patients. The equivalent figure for oral azelastine 4.4 mg/day assessed after 29 days was 8.02 μg/L. The estimated systemic exposure to the intranasal drug was 6- to 8-fold lower than that with oral azelastine.[85-87] A systemic bioavailability of 40% has been shown following intranasal azelastine administration.[84] Unfortunately, the recipient group (i.e. whether patients or healthy volunteers) in the study was not defined. Azelastine is metabolised by the cytochrome P450 enzyme system to its major active metabolite, desmethylazelastine. At steady-state, the plasma metabolite concentration accounts for 20–50% of the azelastine concentration.[88] No data are currently available on the elimination half-life of intranasal azelastine.[56]

Topical antihistamines, such as azelastine, have the specific advantage of delivering high concentrations of the drug more effectively into the target organ while avoiding or minimising systemic adverse effects. In postmarketing surveys, including a total of 7682 patients between the ages of 3 and 85 years who were treated with intranasal azelastine (one spray into each nostril twice daily) for a period of 14 days or 31 days, the most common adverse effects reported by 4002 of the patients 31 days post-treatment included rhinitis (4%), taste disturbance (2.5%) and nasal irritation (1.2%).[89] Other effects including somnolence, dry mouth, epistaxis and headache occurred in <1% of patients. With intranasal azelastine administration as monotherapy in one study, 8% of patients reported adverse events. This figure rose to 20% when intranasal azelastine was combined with other oral antihistamines and/or topical nasal corticosteroids.[90]

Azelastine is generally well tolerated in clinical trials, with a physician and/or patient global assessment of tolerability (where stated) of at least 'good' in >70% of patients (adults and children aged ≥7 years) receiving intranasal azelastine (one puff into each nostril twice daily).[73,77,79,81,91] Good tolerability of azelastine is also generally evident in clinical trials of up to 6 months' duration,[91] with long-term studies also confirming this. For example, one study with intranasal azelastine in 35 patients over a period of 21 months reported that >90% of the participants rated the tolerability of the medication as at least 'good'.[92] The most frequently reported adverse events associated with the use of intranasal azelastine included taste disturbance,[65,66,71,73,93,94] and nasal irritation.[72,76,79,95] The taste disturbance, often short lasting,[63,95] was associated with the drug trickling down the throat, rather than a systemic adverse effect.[65,66,93]

Azelastine appears to be well tolerated in the paediatric population as well. In a study involving 62 children treated with azelastine (0.56 mg/day for 6 months),[91] the most frequently reported adverse events were sneezing (16%), nasal itching (11%), bitter taste (11%) and nasal dryness (9.6%).The tolerability was rated as at least 'good' by the investigators in 74% of participants.[91]

Treatment withdrawal due to azelastine-related adverse events was infrequent, occurring in ≤7% of patients receiving therapy (range of 1–3 patients per study). Reasons for withdrawal included nasal itchiness, congestion, nausea, vomiting, dizziness and hypertension.[64,72,78,80] In clinical trials, the overall tolerability of intranasal azelastine was comparable with that of oral cetirizine,[77,78] intranasal budesonide,[73,74] and intranasal levocabastine.[76]

3.3 Specific Safety and Tolerability Issues

3.3.1 CNS Effects

To date, there have been no formal objective studies investigating the effect of topical azelastine on the CNS in humans. However, animal studies have not shown azelastine to have any significant effect on spontaneous electroencephalogram activity or the susceptibility of the ascending reticular activating system.[55,96] Although sedation secondary to treatment with intranasal azelastine has been reported in some studies, its incidence was not significantly different when compared with placebo controls.[65,66,93,95] When compared with other oral H_1 receptor antagonists such as ebastine[79] and cetirizine,[77] azelastine was associated with significantly less incidence of sedation. In addition the results of some studies have even suggested that intranasal azelastine improved overall alertness and vigilance.[71,90,97,98] It has been suggested that somnolence may be a feature of the rhinitis rather than the treatment. Nevertheless, since some patients in clinical trials have reported somnolence, the US prescribing recommendations include a warning regarding the concurrent use of such medication and driving or operating potentially dangerous machinery. Concurrent use of alcohol and/or other CNS suppressants is not recommended because of possible potentiation of the sedative effect.[88]

3.3.2 Cardiovascular Effects

Cardiac adverse effects, including serious ventricular arrhythmias that can be fatal, have been described for the second-generation oral H_1 receptor antagonists terfenadine and astemizole. However, this is not a class effect and depends on their ability to interfere with the potassium rectifier current in the heart with consequent prolongation of the QTc interval on the ECG.[99] These risks are present only when these agents are either taken in overdosage, or in the presence of impaired liver function, or with the concomitant administration of compounds that compete with the enzyme cytochrome P450, such as macrolides (e.g. erythromycin) and azolic antifungals (e.g. ketoconazole), which results in an increase in the plasma levels of terfenadine and astemizole. A similar effect has also been noted during concomitant ingestion of grapefruit juice.[100] No such adverse events have been reported with azelastine, although there is a paucity of peer-reviewed literature on this aspect. One abstract reported that in a double-blind trial, in which perennial rhinitis patients were randomised to receive azelastine (two puffs per nostril) or placebo twice daily for 8 weeks, no significant changes were found in the following

parameters: mean heart rate or blood pressure, or PR, QS, QT or QT_c intervals on ECG.[101] Age did not appear to influence any of the results. No specific interactions have been reported between intranasal azelastine and oral erythromycin or ketoconazole.[88,102]

3.3.3 Use in Pregnancy

There are no data to support any association between azelastine administration in pregnancy and the incidence of congenital malformations. Therefore, the use of topical azelastine is not specifically contraindicated during pregnancy.[54]

3.3.4 Other Effects

No evidence exists of carcinogenicity or tumour progression in patients taking antihistamines of any form.[55]

4. Intranasal Corticosteroids

4.1 General Overview

Beclomethasone, the first topical corticosteroid for the treatment of seasonal allergic rhinitis, was introduced in 1973 as a nasal spray.[103] Over the following two decades, several other intranasal corticosteroids have been developed and marketed. These include budesonide, flunisolide, fluticasone propionate, mometasone, triamcinolone, and more recently ciclesonide.[5] The commercial availability of these products is very much country-dependent.

The introduction of intranasal corticosteroids represented a revolutionary concept at the time in that it substantially enhanced the therapeutic and safety profiles of these agents because these could be administered topically. The rationale for using intranasal corticosteroids in the treatment of allergic rhinitis was that high drug concentrations could be achieved at receptor sites in the nasal mucosa, with only a minimal risk of systemic adverse effects.[5] At the molecular level, corticosteroids mediate their effect by binding to a single glucocorticoid receptor (GR), which is predominantly localised to the cytoplasm of target cells. The effect on inflammatory cells is mediated via the activation of this GR, which, following translocation to the nucleus, either promotes or inhibits gene transcription through processes known as transactivation and transrepression, respectively.[104] Through this activity, corticosteroids exert anti-inflammatory effects by influencing cytokine and mediator release, thereby modifying inflammatory cell recruitment within target organs, such as the nose. intranasal corticosteroids reduce cell recruitment within the nose and reduce the epithelial accumulation of mast cells, eosinophils and antigen presenting cells, through modifying endothelial and epithelial cell activation. This anti-inflammatory effect underlies the identification of reduced levels of mediators, such as histamine, tryptase, prostanoids, and leukotrienes in nasal lavage fluid after treatment with nasal corticosteroids in allergic rhinitis. Topical therapy with intranasal corticosteroids has also been shown to inhibit the seasonal increase in serum levels of circulating pollen-specific IgE antibodies.[5] It is this widespread effect on various stages of the allergic inflammatory process that underlies their efficacy in allergic rhinitis.

Intranasal corticosteroids are currently recognised as the most potent and effective topical medication available for the treatment of allergic rhinitis, and their superior efficacy in treating this condition has been substantiated in many clinical trials. In three international reports on the management of allergic rhinitis, intranasal corticosteroids were considered as the first-line therapeutic choice for adults with moderate to severe seasonal or perennial allergic rhinitis.[105-107] The regular prophylactic use of intranasal corticosteroids is effective in reducing nasal blockage, rhinorrhoea, sneezing and nasal itching in adults and children with seasonal and perennial allergic rhinitis.[5] A meta-analysis has shown that intranasal corticosteroids are more efficacious than oral H_1 receptor antagonists in reducing the symptoms of allergic rhinitis, with the advantage being most obvious for nasal blockage.[108] A superior clinical efficacy has also been established for intranasal corticosteroids compared with intranasal H_1 receptor antagonists[109] and intranasal sodium cromoglycate.[110,111] Intranasal corticosteroids are equally effective in patients with seasonal or perennial allergic rhinitis. Although small differ-

ences exist in some trials, current evidence does not support any significant overall differences in efficacy between different intranasal corticosteroids when they are administered at dosages adjusted for their differing potencies.[112] The prominent effect of intranasal corticosteroids on nasal blockage, in conjunction with their anti-inflammatory properties,[107] makes them stand out among other available treatments, especially in perennial rhinitis and chronic disease states in which nasal obstruction is a particular problem. It has also been reported that intranasal corticosteroids, even when applied topically to the nose, have effects comparable with oral H_1 receptor antagonists in modifying conjunctivitis in seasonal allergic disease,[108] and may also modify disease expression within the lower airways, with reports of a beneficial effect on both bronchial hyper-responsiveness and symptoms in coexisting asthma.[113-118] The majority of these effects, however, are associated with intranasal beclomethasone. Beclomethasone may differ from some other intranasal corticosteroids in its systemic bioavailability (*vide infra*) therefore, it is uncertain whether these extranasal effects reflect disease modification within the nasal mucosa influencing disease at other sites, or alternatively, represent a direct systemic effect of intranasally administered treatment.

Although intranasal corticosteroids are considered to have a slower onset of action than H_1 receptor antagonists (≥12 hours), maximum efficacy tends to develop over a period of days and weeks.[119-121] Intranasal corticosteroids should be taken regularly in seasonal allergic rhinitis,[122] and, in patients in whom quality of life had been adversely affected in previous years, treatment should ideally be commenced prior to the start of the pollen season for maximal effect.[107] A once-daily regimen is normally sufficient in most cases and is associated with good patient compliance.[123-125] Twice-daily administration may be indicated in severe cases and during exacerbations. The recent ARIA document[5] recommends intranasal corticosteroids as first-line treatment in moderate-to-severe allergic rhinitis. With intermittent symptoms in mild persistent disease, H_1 receptor antagonists are a reasonable choice, either an H_1-antihistamine or an intranasal corticosteroid is recommended as first-line therapeutic option, with the additional consideration of a step up to an intranasal corticosteroid if an H_1-antihistamine is first selected and later found to inadequately control symptoms.[5] The common clinical practice of combining intranasal corticosteroids and oral antihistamines in the treatment of allergic rhinitis is not supported by clinical evidence. Since the combination does not appear to increase the efficacy beyond that of an intranasal corticosteroid used alone,[112,126] therefore, can not be justified as a cost-effective option. It is thought that, *in vivo*, the anti-inflammatory effects of intranasal corticosteroids on the upper airway may encompass the effects of the H_1 receptor antagonists, making the effect of the latter insignificant.

Most of the intranasal corticosteroids formulations nowadays are administered via mechanical aqueous pump sprays or as dry powder, with effective and safe delivery systems. The choice of formulation is dependent on the patient's personal preference.[5]

4.2 Pharmacokinetic Considerations

The pharmacokinetic consideration with a topical therapy in allergic rhinitis is its potential for systemic bioavailability following nasal administration, a process dependent upon factors such as the properties of the pharmacological molecule, its mode of delivery, the influence of the disease state, and the fate of the absorbed molecule once within the circulation, which will be influenced by factors such as its volume of distribution, metabolism and excretion profiles. The net potential of any agent will depend upon the balance between these factors. When only one factor is focused on, e.g. drug potency or drug lipophilicity, there may be a misapprehension as to the likelihood of systemic adverse effects from an intranasally administered corticosteroid. However, since intranasal administration is an important route of systemic absorption that bypasses the protective effects of first-pass metabolism, consideration of the factors affecting systemic bioavailability has assumed greater significance over the past decade,

particularly with the increased availability of newer and more potent topical corticosteroids. In the absence of a change in any other determinant, an increase in potency to achieve an enhanced therapeutic benefit could also be paralleled by an increased potential for systemic adverse effects. It is essential, therefore, to be aware of the pharmacokinetic properties of the different intranasal corticosteroids and their potential for systemic effects, in addition to how the newer drugs compare with the older ones.

Each nasal cavity has a volume of approximately 10mL and the combined nasal mucosal surface area of both nasal cavities for drug absorption is about 180cm^2. The physicochemical properties of a drug that determine its absorptive properties from this site include its molecular weight, lipophilicity and particle size. There is an inverse relationship between molecular weight and rate of absorption, with those molecules with a molecular weight of <300 kDa being significantly less influenced by their physicochemical properties and more readily absorbed, while those with >1000 kDa exhibit little absorption. Apart from ciclesonide, which is a prodrug with a molecular weight of 260 kDa, all the other intranasal corticosteroids have molecular weights that range between 430–530 kDa, with the following rank order: budesonide (430.5 kDa), flunisolide (434.5 kDa), triamcinolone (434.5 kDa), fluticasone propionate (500.6kDa), beclomethasone (521.25 kDa), mometasone (521.4 kDa). Thus, there is little difference in the molecular weights of these corticosteroids, and this factor is not crucial in determining differences between their absorption profiles. Although lipophilicity is an important determinant of the ability of a molecule to cross an epithelial barrier, it also determines the tissue retention of the molecule. Fluticasone propionate, which has a high lipophilicity, has been found to exhibit the highest epithelial tissue concentration after *in vitro* incubation in a comparison with budesonide, flunisolide and beclomethasone-17-monopropionate.[127] Metabolism within the tissue site will modify the fraction available for systemic bioavailability and thus any potential for systemic adverse effects. Budesonide undergoes nasal metabolism, in that it is esterified within the nasal tissue, forming pharmacologically inactive, intracellular fatty acid, oleate and palmitate esters.[128] Budesonide is, however, released from these esters by the action of lipases, so this metabolism allows budesonide to have a more prolonged tissue residency than would be anticipated from its lipophilicity profile, but does not bar the drug from eventual bioavailability. The presence of cytochrome P450 isoenzymes within the nasal mucosa may account for the lower bioavailability of both fluticasone propionate and mometasone from this site *(vide infra)* than would be anticipated on the basis of lipophilicity profiles alone, as both these corticosteroids are converted to inactive metabolites in the presence of these enzymes. The hepatic metabolism by these enzymes accounts for the first-pass metabolism of these particular corticosteroids that prevents their systemic bioavailability by the oral route.

The type of delivery device for nasal administration has also been shown to influence the potential for systemic bioavailability. Pressurised metered dose inhalers (pMDIs), aqueous pump sprays and a powder inhaler have been used to topically administer nasal corticosteroids. The aerosol generated from a pMDI has a high velocity and is highly directional, resulting in a narrow proximal deposition in the nasal cavity.[129] Comparatively, the aerosol from an aqueous pump spray displays a large droplet size with a more dispersed pattern of deposition.[130] The nasal distribution pattern with a powder inhaler lies somewhere between the other two devices.[131] A study investigating the systemic availability of various formulations of intranasal budesonide[132] showed a significantly higher absorption level with the aqueous pump spray compared with the pMDI and powder formulations. Following the Montreal agreement, pMDIs are no longer used for nasal administration because of the CFC propellant, and aqueous nasal spray is now the recommended standard delivery device in the treatment of allergic rhinitis. An additional delivery mode, nasal drops, are licensed for use in nasal polyposis and have been used off-label by allergists and rhinologists for the

treatment of severe rhinosinusitis as an alternative to low-dose prednisolone therapy, particularly following endoscopic sinus surgery. These formulations contain higher doses of corticosteroid than are used with nasal spray administration and have caused concern as to their potential for systemic adverse effects, although this is a lesser consideration if they are being used in a situation in which oral prednisolone would otherwise be given. One such formulation is fluticasone propionate nasal drops, Flixonase Nasule®[1], which is licensed for use in Europe at a dose of up to 1600μg daily. It is currently not licensed for use in the US. A recent study investigating the systemic bioavailability of fluticasone propionate administered either as nasal drops or as an aqueous nasal spray formulation, using a sensitive analytical method and a high dose regimen, found that both formulations exhibited low systemic bioavailability, even at 12 times the normal daily dosage.[133] Interestingly, the bioavailability of fluticasone propionate nasal drop formulation (0.06%) was approximately eight times lower that that of the nasal spray (0.51%), which may be explained by the findings that nasal drops are cleared more quickly from the nose than nasal sprays.[134,135]

Another consideration is whether the inflammatory disease process itself has any effect on the absorption of the drug from the nose. It might be anticipated that an inflamed nasal mucosa, with an impaired epithelial barrier, might permit greater systemic absorption than the normal nasal mucosa. Thus, nasal bioavailability studies undertaken in healthy volunteers may not reflect the situation in allergic rhinitis, and may underestimate the potential for nasally administered corticosteroids to produce systemic adverse effects. However, the available evidence to date suggests otherwise. A study investigating the effects of acute and chronic intranasal administration of therapeutic doses of triamcinolone to subjects with active allergic rhinitis, found no significant effect of the nasal mucosal inflammation on the absorption of intranasal triamcinolone.[136] A further study investigating the nasal absorption of desmopressin found no difference between those with house dust mite perennial allergic rhinitis and healthy controls, leading to the conclusion that nasal absorption is unaffected by the disease state in allergic rhinitis.[137] Thus, there is seems no basis for the added concern in allergic rhinitis as to the potential for topical nasal corticosteroids to induce systemic adverse effects.

Once absorbed, the corticosteroids will be distributed within the body fat in relationship to their lipophilicity and will be in equilibrium with the blood, so that as clearance takes place from the blood there will be clearance from the tissue. The greater volume of distribution of the most lipophilic corticosteroids, such as fluticasone propionate and mometasone, has been put forward as a potential risk factor for systemic adverse effects, with the suggestion that the low plasma concentrations with these corticosteroids after intranasal administration gives a false representation of their true systemic bioavailability.[138] This argument is neither supported by the more recent work on urinary cortisol measurements with intranasal mometasone administration,[139] nor by analysis of previous data involving fluticasone propionate in comparison with triamcinolone, when the results are appropriately corrected for urinary creatinine.[140] Indeed, this argument does not stand up to critical appraisal on theoretical grounds, even in the absence of these findings. Despite fluticasone propionate being more lipophilic and having a higher volume of distribution (318L) than the less lipophilic triamcinolone (103L), both of these values are still greatly in excess of the blood volume (5L) and, at steady-state, approximately 98% of fluticasone propionate and 95% of triamcinolone will be in the tissue. With the published bioavailability data for fluticasone propionate and triamcinolone of 0.5% and 46% respectively, at steady-state with standard dosage this would lead to respective tissue doses of 0.7μg and 46μg. Although it will take longer to clear fluticasone propionate than triamcinolone from the tissue once treatment stops, because of the longer half-life of fluticasone, this is irrelevant, as for a substantial period the tissue concentrations of triamcinolone

1 Use of the registered name is for identification purposes only and does not imply endorsement.

will remain in excess of fluticasone propionate because of the because of the higher starting level. Thus, despite lipophilicity being a determinant of tissue concentrations, it does not necessarily follow that more lipophilic corticosteroids have a greater potential for adverse effects. This is because there are other factors, including the percentage of administered drug that is available for systemic delivery, which determine the systemic adverse potential of intranasal corticosteroid due to the activation of tissue GRs. Prior to predicting the potential for newer corticosteroids to induce adverse systemic effects, it is therefore necessary to have access to all such information in order to make an informed judgement.

4.3 Tolerability and Safety Profile

4.3.1 Local Effects

Currently available intranasal corticosteroids are generally well tolerated. Occasional local adverse effects include irritation of the nose and throat, and sneezing bouts because of localised irritation from nasal administration, particularly at the start of the treatment.[141] Other potential adverse effects include crusting, transient dryness, minor epistaxis and, rarely, ulceration.[121,125,142-144] These tend to be self-limiting, but are occasionally persistent, and a change to a different formulation or delivery system may be needed in order to eliminate them. The risk of a septal perforation, albeit minimal, is significant considering the serious implications associated with this. The risk of a perforation appears maximal during the first year of treatment, with mostly young females being affected. The risk is compounded by a history of previous nasal surgery, or erroneous application methods, particularly when the spray or drops are directed towards the nasal septum. It is good practice for prescribing clinicians to advise patients to aim the spray well away from the midline.[145,146] The risk of developing atrophic rhinitis has not been proved.[121] Contact allergic reactions of the skin and mucosa to intranasal corticosteroids are rare, but have been described.[147,148]

4.3.2 Effects on Hypothalamic-Pituitary Adrenal Axis and Growth

The basic principle in measuring the potential systemic bioactivity of corticosteroids is to evaluate a biomarker of an activity that is influenced by exogenous corticosteroid administration, such as suppression of endogenous cortisol secretion from the adrenal cortex.[149] There are currently two basic types of measurements. The first relates to the basal adrenocortical secretion, while the second represents a measure of the dynamic function of the hypothalamic-pituitary adrenal (HPA) axis in order to establish the level of adrenal reserve. Although measurement of the basal levels of adrenocortical secretion is fairly simple in principle, it does possess some inherent disadvantages, particularly in relation to the underlying variation in secretion levels due to the normal circadian rhythm (highest in the morning and lowest around midnight). Thus, variable sampling times could potentially lead to high variability in results and a reduced sensitivity of the test. Nevertheless, this test remains a very simple and relatively reliable method as long as the sampling time is standardised.[138] The most sensitive methods for measurement of basal adrenocortical function are those that integrate either 24-hour or overnight cortisol output as reflected by urinary measurements on samples collected over this time period. This integrated approach towards measurement is very important, particularly as corticosteroids with different pharmacokinetic properties can affect the HPA axis at differing time points during the dosing interval.[138]

The interpretation of dynamic function tests of adrenocortical activity needs to be evaluated within the context of the stimulating dose of corticotropin (adrenocorticotropic hormone). This is because the frequently used dose of corticotropin (250μg) represents a supraphysiological dose that can render the test less sensitive.[138] It is generally accepted that lower doses of corticotropin (0.5–1μg) are as effective in producing a stimulated cortisol response and tend to improve the sensitivity of the test.[150] There are also other issues that need to be considered, particularly when interpreting the results of these types of studies. These include, the issue of whether

the study drug was administered for long enough to reach steady-state levels, issues pertaining to the dosage (e.g. recommended vs higher than licensed dosage), characteristics of the study population (e.g. healthy volunteers vs patients with allergic rhinitis), state of activity (e.g. sedentary vs normal day activity study), duration and timing of the urine collection period (e.g. 12-hour vs <12-hour collection period), method of cortisol assay (e.g. radioimmunoassay vs liquid chromatography tandem mass spectrometry), method of statistical analysis of results (e.g. use of conventional vs unconventional statistical tests), and, importantly, whether the study was adequately powered. The latter consideration is particularly important when comparisons are made between active therapies. It is understandably essential that these and other limitations are considered in determining the validity and strength of any conclusions. Although the influence of intranasal therapy on the HPA axis is the evaluation most often used for determining the bioavailability of systemic corticosteroids, other evaluations on bone turnover with osteocalcin, or bone growth with knemometry, have also been employed.

There is still concern that the continued and, in some cases, prolonged use of intranasal corticosteroids may be associated with systemic adverse effects, including suppression of the HPA axis and an effect on growth. This complicates the use of oral and, in some cases, inhaled corticosteroids for the treatment of asthma. Certainly, the introduction of intranasal formulations has reassured, but has not completely dispelled these fears. For instance, dexamethasone spray and betamethasone drops can rarely provoke systemic effects.[151-155] Additionally, the dosage at which clinically relevant systemic adverse events occur remains controversial.[156,157]

A small number of studies have suggested significant effects of intranasal corticosteroids on the HPA axis.[158,159] Despite such isolated studies, the overwhelming clinical and pharmacokinetic evidence in the published literature to date clearly supports the view that intranasal corticosteroids are unlikely to cause any significant suppression of the HPA axis when administered short-term at the recommended therapeutic dosage.[121,140,160-164] Patients exclusively receiving intranasal corticosteroids appear to be at a very low risk of developing HPA axis suppression because of a number of important factors, including the extensive hepatic first-pass metabolism, limited systemic drug availability and the low dosage.[165-167] This is particularly the case with the newer intranasal corticosteroids, including fluticasone propionate, budesonide, triamcinolone and mometasone, which do not appear to have any significant effects on the HPA axis.[121,140,158,162-164,168-171] The addition of intranasal corticosteroids to inhaled corticosteroids does not appear to increase suppression of the HPA axis.[172] It is important to bear in mind that the apparent lack of HPA axis suppression with intranasal corticosteroids does not preclude the occurrence of other systemic adverse effects, particularly as this endpoint may not be the most sensitive index of systemic bioavailability. The risk of such effects is very much dependent on the systemic bioavailability of the corticosteroid used. This can vary widely, by up to 100-fold in some cases, depending on the topical corticosteroid used.[173]

Two studies have described an effect on children's growth relating to intranasal beclomethasone and budesonide administration.[174,175] These studies did not necessarily indicate a class-specific effect, however, as there were important differences between the varying intranasal preparations and their systemic bioavailability with intranasal application. At the time of these studies, however, there was limited prospective information and, as a precaution, the FDA felt it appropriate to recommend that all intranasal corticosteroids within the US were labelled with a warning that their use in children may adversely affect growth. Beclomethasone has the highest gastrointestinal absorption of the corticosteroids used in the treatment of asthma (relevant on account of the high proportion of swallowed drug from metered dose administration) and, as a nasal corticosteroid, has a bioavailability of 44%,[176] second only to triamcinolone in the currently available intranasal spray preparations. An effect on growth, albeit small, is thus likely to be a reflection

of systemic bioavailability with intranasal beclomethasone when it is administered at its standard recommended dosage for a prolonged period (one year in this study).[174] Budesonide has a lower systemic bioavailability, and the report of an effect of intranasal budesonide on growth stemmed from the administration of the adult dose of 200μg twice daily. Moreover, this result could not be reproduced in another study investigating the effect of budesonide 400μg daily on child growth assessed by lower leg knemometry.[177] Compared with placebo, the study failed to find any inhibitory effect on the short-term growth rate of the children involved. The situation with budesonide is thus not so clearcut. More prospective data is urgently required to further evaluate the safety profile of intranasal corticosteroids in young children.[157] The current recommendation of the Committee on Safety of Medicines in the UK is that the height of children receiving prolonged treatment with nasal corticosteroids should be monitored. If growth appears to be inhibited or slowed, then a paediatric referral should be considered.[82]

The newer topical corticosteroids, such as mometasone and fluticasone propionate, have a substantially reduced systemic bioavailability (<1%), particularly when administered nasally, compared with some of the older corticosteroids, such as beclomethasone and budesonide. Prospective studies with mometasone and fluticasone propionate have not identified any adverse effect on growth when used at standard doses in children.[178] Consequently, the potential for systemic effects can be substantially reduced by careful selection of the intranasal corticosteroid.[176,178,179]

4.3.3 Other Systemic Effects

Smell and taste disturbances and hypersensitivity reactions, including bronchospasm, have been reported to rarely occur.[82] Although adverse effects such as dermal atrophy, cataract formation, glaucoma, metabolic changes, and behavioural abnormalities have been reported in patients receiving corticosteroids administered via other routes, there are no reports to date that link such effects to corticosteroids administered solely via the nasal route.[156]

4.3.4 Use in Pregnancy

There are currently no data to substantiate any association between intranasal corticosteroids and congenital malformations. Inhaled corticosteroids such as beclomethasone or budesonide[180] are not thought to have potential teratogenic or embryotoxic effects, and are used widely by pregnant women with asthma. Although the choice of agents should be based on evidence of fetal safety, the issues of efficacy and maternal health also need to be considered in order to optimise any management plan.[110]

5. Specific Corticosteroids

5.1 Beclomethasone

Beclomethasone has been reviewed by Edelman and van Os.[181] It has a slow gastrointestinal absorption and a rapid first-pass inactivation by the liver.[182] The absolute bioavailability of intranasal beclomethasone is 44%.[176,183] Intranasal dosage of up to 400 μg/day of beclomethasone have not been associated with suppression of the HPA axis when given for up to 6 months.[166,182] However, when used at twice the recommended therapeutic maximal dosage (800 μg/day), beclomethasone was found to reduce urinary cortisol.[184] Despite not having any significant effect on the HPA axis, 12 months' treatment with beclomethasone (mean dose 168μg twice daily) was reported to exert a small but significant ($p < 0.01$) effect on the growth of 6- to 9-year-old children with a mean growth velocity of 4.78 cm/year compared with 6.11 cm/year for the placebo group. This difference of 1.33 cm/year was found to be statistically significant ($p < 0.01$).[185]

A small case series has demonstrated a low incidence of cataracts related to the use of inhaled and intranasal beclomethasone.[186] This case series included 21 spontaneous reports of posterior subcapsular cataracts in patients receiving either intranasal or inhaled corticosteroids. Nine patients were also receiving systemic corticosteroids, which could have influenced the risk of developing cataracts. There were also limitations in this study pertaining to the paucity of details provided, particularly in relation to the dosage and duration of therapy. A

further large-scale observational cohort study of patients aged <70 years, showed the incidence of cataracts following intranasal beclomethasone use was 1/1000 person-years,[187] similar to the incidence rate in the nonusers. However, recipients of oral corticosteroids were at a higher risk of cataract (2.2/1000 person-years). In the UK register of spontaneously reported adverse drug reactions, two cases of cataract associated with the use of intranasal beclomethasone have been reported, representing 0.56% of all reports of cataracts in the UK.[157] For cataract and intranasal corticosteroids, the proportional reporting ratio (PRR) was 5 with a χ^2 of 6.39 ($p < 0.0115$). Despite the significant PRR, the evidence presented overall in the literature certainly does not currently support an association between intranasal corticosteroids and an increased risk of developing cataracts. The raised PRR is probably indicative of a theoretical risk particularly with prolonged high dose therapy.[157] Further studies are required to substantiate these findings.

A large case-controlled study of elderly patients receiving either beclomethasone or fluticasone propionate, did not find an increased risk of developing raised intraocular pressure or low-angle glaucoma.[188] This applied to both low-to-medium doses and high doses of the inhaled corticosteroids. According to manufacturer's data on file only 25 cases of glaucoma/raised intraocular pressure were reported in patients treated with intranasal beclomethasone between 1975 and 1996.[189]

Intranasal beclomethasone has not been found to have a detrimental effect on nasal mucosa or physiology. Rhinoscopic and histopathological examination of the nasal mucosa after 12 months of treatment with intranasal beclomethasone did not reveal any evidence of adverse effects.[190] Electron microscopic analysis of 142 nasal biopsies showed no detrimental effect on the nasal mucosa following 9–36 months of treatment with intranasal beclomethasone (400 μg/day).[191] Septal perforation is a rare complication following the use of intranasal beclomethasone. This has been confirmed in literature reviews.[142,182] According to manufacturer's data on file only 70 cases of septal perforation were reported following the use of intranasal beclomethasone between 1974 and 1996.[189]

The use of intranasal beclomethasone during pregnancy and lactation is not advised by the manufacturer as no prospective studies have been undertaken under such circumstances.[192] A record linkage study has suggested, however, that the rate of congenital malformations in women exposed to beclomethasone during the first trimester does not exceed background rates.[54] The Beconase® patient information leaflet for the non-prescription product advises the consumer to seek advice from their doctor prior to using intranasal beclomethasone during pregnancy.[193]

The local adverse effects associated with intranasal beclomethasone are minimal and include dryness/irritation of nose and throat, unpleasant taste and smell, headache and minor epistaxis. Rare cases of raised intraocular pressure or glaucoma have been reported in association with intranasal beclomethasone administration. The overall reporting frequency for adverse events is very low (approximately 0.18 events per estimated 1000 patient-years).[189,192] There have been no reported incidences of overdose with intranasal beclomethasone. However, it has been shown that at a dosage of 8 mg/day, intranasal beclomethasone did have an effect on the HPA axis in some but not all subjects, with a return to normality after 48 hours.[194] No other local or systemic adverse effects have been reported to date.[5]

5.2 Budesonide

Budesonide aqueous nasal spray has a systemic bioavailability level of 31%.[176] In an open 12-month study, intranasal budesonide used in the treatment of vasomotor (perennial non-allergic) rhinitis at a dose of 400 μg/day did not lead to any significant changes in haematological, biochemical or plasma cortisol levels.[195] The long-term safety and tolerability of intranasal budesonide (200–400 μg/day) has been substantiated over a 12-month period, in which it was not found to cause either nasal mucosal atrophy or suppression of the HPA axis.[196] In a study lasting up to 5.5 years, the

continued use of budesonide nasal aerosol had no measurable effect on the HPA axis and did not alter the nasal epithelium.[197] At a daily dosage of 200μg, intranasal budesonide has not been found to have an effect on the HPA axis.[140,158] One multidose study did report a reduction in urinary cortisol with the use of intranasal budesonide at a daily dosage of 200–800μg.[184] Using knemometry, it was shown that 4-week treatment with intranasal budesonide (200–400 μg/day) did not significantly affect growth velocity, although a trend toward reduction was seen with the 400 μg/day dosage.[176] However, in another study comparing terfenadine (60 mg/day), intranasal budesonide 200 μg/day, and depot methylprednisolone 60mg, a significant reduction in growth velocity was observed over a 6-week period in those children receiving the nasal and systemic corticosteroids.[198] No other local or systemic adverse effects have been reported to date.[5]

5.3 Ciclesonide

Ciclesonide is a new, non-halogenated topical corticosteroid with anti-inflammatory properties,[199] that has recently been found to be effective in the treatment of allergic rhinitis (dose of 200μg into each nostril), and has displayed excellent local and systemic tolerability profiles.[200] A recent placebo-controlled, randomised, double-blind study assessed the influence of inhaled ciclesonide on the circadian time serum cortisol rhythm, and concluded that at a daily dosage of 800μg for 7 days, inhaled ciclesonide did not exert any significant effects on the HPA axis.[201] The systemic bioavailability of intranasal ciclesonide is currently unknown. There have been no reports of systemic adverse effects related to the use of topical ciclesonide to date.

5.4 Flunisolide

Flunisolide aqueous nasal spray has a systemic bioavailability level of 40–50%.[202] No effects of intranasal flunisolide on the HPA axis or growth have been reported to date. A recent 1-year trial evaluating the safety profile of flunisolide hydrofluoroalkane in children with asthma reported no adverse effects associated with HPA axis function, including linear growth in 6- to 11-year-old children, when compared with beclomethasone and sodium cromoglycate.[203] The excipients, polyethylene glycol and polypropylene glycol, can cause transient local irritation manifesting as a stinging sensation.[5] No other local or systemic adverse effects have been reported to date.[5]

5.5 Fluticasone Propionate

The pharmacokinetic profile of intranasal fluticasone propionate minimises the potential for systemic adverse effects. It is estimated that the major portion of the dose is cleared by the nasal cilia and eventually swallowed.[204] Fluticasone propionate aqueous nasal spray has a systemic bioavailability of 0.42–0.51%.[133,176] In view of the low systemic bioavailability and the low therapeutic doses used, there is a low risk of developing suppression of the HPA axis. Although the findings in one study in healthy volunteers suggested that intranasal fluticasone propionate administration was associated with a clinically significant suppression of urinary cortisol,[158] this has not been reported by extensive studies in patient populations (see section 4.2 for a more detailed discussion concerning intranasal corticosteroid bioavailability, particularly in relation to fluticasone propionate). The effects of intranasal fluticasone propionate on HPA axis function were investigated by analysis of morning plasma cortisol concentrations, response to corticotropin and 24-hour urinary free-cortisol excretion.[205] There was no evidence of effects on adrenal function, even at high doses of intranasal fluticasone propionate. Other studies have not found intranasal fluticasone propionate to have an effect on the HPA axis at a daily dose of 200μg in adults[115,164,178,206] or children.[169,207] The overwhelming evidence in the literature regarding the short-term intranasal use of therapeutic doses of intranasal fluticasone propionate certainly backs its clinical safety in that respect.[208] Intranasal fluticasone propionate has not been found to have a significant effect on growth. A study comparing intranasal fluticasone propionate treatment with placebo showed the two groups to be comparable in terms of longitudinal leg growth in a

2-week study in children using knemometry.[209] Inhaled fluticasone propionate has not been shown to have any adverse effects on the growth of children in studies over a period of 12 months.[210]

Intranasal fluticasone propionate use has not been associated with any ocular adverse effects. A large case-controlled study of elderly patients using either beclomethasone or fluticasone propionate did not find an increased risk of developing raised intraocular pressure or low-angle glaucoma.[188] This applied to both low-to-medium doses and high doses of the inhaled corticosteroids. There was no evidence of posterior subcapsular cataracts or glaucoma in patients treated for 1 year with intranasal fluticasone propionate at a dose of 200 μg/day.[208]

There has been one report in the literature of a possible link between intranasal fluticasone propionate administration and the onset of benign intracranial hypertension in a 13-year-old boy.[211] However, it must be stressed that this was an isolated report with poor adherence to the strict diagnostic criteria for this condition. To date, a cause-effect link has yet to be firmly established.

There is no evidence of intranasal fluticasone propionate having any detrimental effect on the nasal mucosa or physiology. Nasal biopsies performed following 12 months of treatment with intranasal fluticasone propionate (200 μg/day) did not reveal any abnormalities on histopathological examination.[121,212] There has recently been controversy regarding the possible ciliostatic effect of benzalkonium chloride, a preservative used in many nasal sprays, on human nasal epithelium *in vivo*. A single-centre, double-blind nasal biopsy study in 22 patients receiving intranasal fluticasone propionate containing benzalkonium chloride, using scanning and transmission electron microscopy examination, found no evidence of such an effect of benzalkonium chloride *in vivo*, when it was applied for 6 weeks (with/without fluticasone propionate) to the nasal mucosa of patients with perennial allergic rhinitis.[213] Intranasal fluticasone propionate has also been shown to have no detrimental effect on nasal physiological parameters following 12 months of treatment at a dose of 200 μg/day.[214] The incidence of septal perforation associated with intranasal fluticasone propionate use is rare, except in the presence of other predisposing factors.[215]

The use of intranasal fluticasone propionate during pregnancy and lactation is not advised by the manufacturer as no prospective studies have been undertaken under such circumstances. There is thus inadequate evidence currently on the safety profile of fluticasone propionate in human pregnancy. In animal reproduction studies, adverse effects typical of potent corticosteroids are only seen following high systemic exposure levels. In the case of direct intranasal application, minimal systemic exposure is ensured.[216,217] The consumer is advised to seek advice from their doctor prior to using intranasal fluticasone propionate during pregnancy.

Considering the very low plasma concentration of fluticasone propionate following intranasal application, clinically significant drug interactions are unlikely.[218] Fluticasone propionate is metabolised by the cytochrome P450 enzyme CYP3A4 to an inactive carboxylic acid metabolite. Therefore, care should be taken when co-administering known strong CYP3A4 inhibitors (e.g. ritonavir or ketoconazole), as there is potential for interaction and subsequent increased risk of systemic adverse effects of fluticasone propionate.[218]

A few local adverse effects have been linked with the use of intranasal fluticasone propionate. These are probably related to the nasal spray itself rather than any active ingredients, and include dryness/irritation of the nose and throat, unpleasant taste and smell, headache, and minor epistaxis. The overall reporting frequency for adverse events is very low, with 0.02% of individuals who have received fluticasone propionate experiencing an adverse event.[216]

There have been few reported incidences of intranasal fluticasone propionate overdose. According to a report from the manufacturer, there were five cases of overdose from 13.1 million patient-years of exposure were reported between March 1998 and August 2001.[219] Incidentally, intranasal fluticasone propionate administered at 20 times the recommended dosage (2mg twice daily) for 7 days, in healthy

adult volunteers, showed no adverse effect on the HPA axis.[204] No other local or systemic adverse effects have been reported to date.[5]

5.6 Mometasone

Mometasone aqueous nasal spray has a systemic bioavailability of 0.46%.[176] In a crossover controlled study,[140] 5-day courses of intranasal mometasone at a clinically recommended dosage (200 μg/day) did not have any significant effect on the HPA axis, bone metabolism or basic haematological parameters. This was confirmed by the results of two further studies.[166,220] Over a 1-year period, treatment of children with perennial rhinitis with intranasal mometasone (100 μg/day) did not appear to suppress the HPA axis or have any inhibitory effect on their short-term growth rate.[178] These findings were paralleled by the results of another study, which failed to detect any effect on the HPA axis in children treated with intranasal mometasone (50, 100, and 200 μg/day) for 7 days.[221] A dose-ranging study of intranasal mometasone in children with seasonal allergic rhinitis concluded that at a dosage of up to 200 μg/day, intranasal mometasone was well tolerated with no significant effects on the HPA axis.[222] The satisfactory safety profile of intranasal mometasone in adults and children with allergic rhinitis has been recently reiterated in reviews[160,223] of the most recent and relevant clinical trials concerning this issue.

A study of adult patients with perennial rhinitis treated for 12 months with intranasal mometasone (200 μg/day) showed no adverse tissue changes in nasal biopsies following treatment.[224] Similarly, no significant effect of intranasal mometasone (200 μg/day) on olfactory function or mucociliary clearance could be detected.[225]

No other local or systemic adverse effects have been reported to date.[5]

5.7 Triamcinolone

Despite having a systemic bioavailability of 46%,[176] intranasal triamcinolone does not appear to cause suppression of the HPA axis. The possible systemic effects of intranasal triamcinolone (110 or 200 μg/day) aqueous nasal spray on the HPA axis were assessed in a study of male subjects with allergic rhinitis.[162] Morning plasma cortisol levels, urinary cortisol, and corticotropin stimulation were evaluated. No significant effect of the nasal corticosteroid on these parameters was found. In another study, no significant changes of morning serum cortisol levels were recorded in 93 patients with allergic rhinitis taking intranasal triamcinolone (110, 220, and 440 μg/day) for >1 year.[226] This finding was further confirmed in one long-term[227] and three medium-term[228-230] studies in adult patients. In a further crossover controlled study,[140] 5-day courses of intranasal triamcinolone at clinically recommended doses did not affect the HPA axis, bone metabolism, or basic haematological parameters. A study conducted in healthy volunteers after a 4-day course of intranasal triamcinolone (220 μg/day) did not report any significant change in overnight urinary cortisol levels.[184] No effect of intranasal triamcinolone was found on serum cortisol or the stimulated corticotropin response in another study.[158] The lack of effect on HPA axis was also established in a study in children.[161] The safety of once-daily administration of intranasal triamcinolone (220 μg/day) for 3 weeks was evaluated in 429 patients with seasonal allergic rhinitis compared with a placebo group.[231] The results showed no significant difference between the two groups. Similar results were obtained in another study.[163] In perennial allergic rhinitis, a multicentre study evaluating the safety of once-daily regimen of intranasal triamcinolone (110, 220, and 440 μg/day) in patients aged between 12 and 65 years demonstrated a satisfactory profile.[232]

Clinical and pathological studies have also been carried out to investigate the long-term effects of intranasal triamcinolone on the nasal epithelium. One such study was a long-term prospective local safety study evaluating the endoscopic and histological changes in the nasal epithelium after a 6-month treatment period with intranasal triamcinolone.[233,234] Results were also compared with those seen with cetirizine and beclomethasone dipropionate. Overall, the results indicated that

long-term intranasal triamcinolone treatment did not result in atrophic changes in the epithelium or impairment of mucociliary function. No other local or systemic adverse effects have been reported to date.[5]

6. Specific Safety and Tolerability Considerations

6.1 Paediatric Population

Although the principles of pharmacological treatment are identical to those in adults, caution has to be exercised in order to avoid adverse events typical in the paediatric population.[107,235] Dosage adaptation and special terms are often necessary, not only because of the age factor, but also to ensure that optimum therapeutic efficacy is achieved.[236,237]

Although often trivialised by parents and doctors, allergic rhinitis is a significant cause of morbidity in the paediatric population, leading to social embarrassment on account of the rhinitis, and on account of the widespread mucosal inflammation affecting several target organs, and a generalised sense of malaise with cognitive function impairment. This can be further compounded by inappropriate antihistamine treatment.[238] For rhinoconjunctivitis in children, intranasal corticosteroids remain the most effective treatment currently available. Although there is a theoretical risk of systemic adverse effects, this has not been shown in practice, particularly with the modern intranasal corticosteroids which have low bioavailability (<30%) with little evidence of significant systemic absorption. It is fairly self-evident that the minimal dose of intranasal corticosteroids should be used when control of symptoms is required. In contrast to the clear inhibitory effect upon growth and growth velocity of oral and depot corticosteroid preparations,[198] the overwhelming evidence does not support a similar effect relating to intranasal corticosteroids administration.[177,178] As previously discussed in section 4.3.2, two studies with intranasal beclomethasone[174] and intranasal budesonide[175] did report inhibitory effects on growth. With this in mind, it is generally agreed nowadays that intranasal corticosteroids with high systemic bioavailability should not be recommended for use in children.[153]

With their action mainly centred on the target organ, and in conjunction with lack of any associated significant systemic effects, the use of intranasal antihistamines, such as levocabastine and azelastine, is clearly advantageous in children. However, despite being safe and useful for relieving nasal/ocular symptoms of allergic rhinitis, the intranasal antihistamines lack the degree of efficacy achieved by intranasal corticosteroids and are thus more appropriate for the treatment of mild or intermittent forms of allergic rhinitis in children, especially where nasal obstruction is not a prominent symptom.[5,20]

6.2 Pregnancy

Allergic rhinitis affects around one-third of women of child bearing age,[54] and is often aggravated by pregnancy.[239-241] Caution must be exercised when prescribing medications to pregnant women, particularly in relation to the potential risk of congenital malformations. A satisfactory safety and tolerability profile in adults does not necessarily rule out such effects in a fetus. Therefore, it is vital when prescribing in pregnancy to consider the benefit/risk ratio for the fetus as well as the mother.[5] Conversely, it must be stressed that in studies pertaining to the possible teratogenic and embryotoxic effects of medications, consideration of the needs of the symptomatic mother for treatments that adequately control the disease, should not be overlooked. Treatment in pregnancy is thus a balance of risk against efficacy, with the balance tilted in favour of safety. Fortunately, topical therapy for the nose has made available an effective treatment modality associated with a minimal risk of systemic adverse effects.

With respect to inhaled corticosteroids, there have been no documented prospective epidemiological studies on their use during pregnancy, but they are frequently used by pregnant women with asthma and have not as yet been incriminated as teratogens.[54] No maternal-fetal adverse effects were

reported in 40 pregnant women with asthma who were treated with beclomethasone.[242]

Although some first-generation antihistamines (e.g. brompheniramine, promethazine, diphenydramine and hydroxyzine) have been shown to be teratogenic in animals,[243,244] there is no evidence for any such effects in humans.[245] Second-generation intranasal antihistamines have not so far been incriminated as human teratogens or embryotoxins and their use during pregnancy is currently not specifically contraindicated.[54]

6.3 The Elderly

Intranasal corticosteroids and topical second-generation antihistamines are fairly well tolerated in the elderly with minimal adverse effects.[5]

7. Conclusion

Taking into account the results of the studies undertaken on intranasal antihistamines and intranasal corticosteroids, it is generally agreed, nowadays, that intranasal corticosteroids are more potent and efficacious in reducing the symptoms of allergic rhinitis than intranasal antihistamines,[246,247] with the particular advantage being most obvious for nasal obstruction.[108,112] The superior efficacy of intranasal corticosteroids is not only evident clinically, but also when one considers other objective parameters, such as inflammatory markers, rhinomanometry, acoustic rhinometry, and quality-of-life assessments.[112,126]

While there exist clear differences in the degree of therapeutic efficacy when intranasal corticosteroids and intranasal antihistamines are compared, no such trend can be identified in the safety/tolerability profiles of these two classes of drugs. Apart from minor qualitative differences in the nature of localised adverse events linked to intranasal corticosteroids (e.g. nasal bleeding) and intranasal antihistamines (e.g. sedation), no significant quantitative discrepancies between the two groups have been found. This is mainly due to a generally low incidence of adverse effects in both treatments.[112] Concern has emerged over the possible effects of intranasal corticosteroids on the HPA axis and growth velocity, however, this risk has not consistently been seen in practice in patients with allergic rhinitis

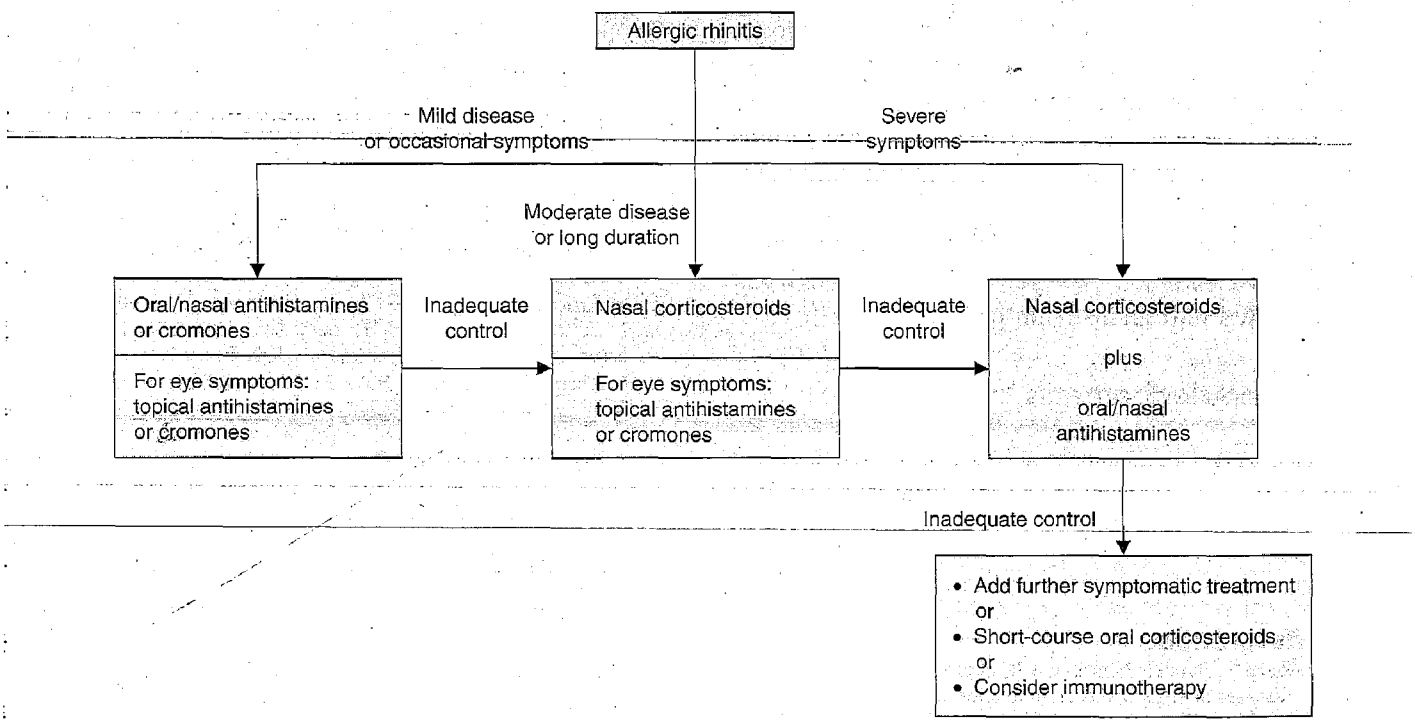

Fig. 1. Algorithm of the management protocol for allergic rhinitis based on the allergic rhinitis and its impact on asthma (ARIA) guidelines.

alone,[28,206,248,249] although only a few studies have prospectively assessed this. The emerging evidence indicates that there may be a small risk with prolonged use with certain nasal corticosteroids. However, the more recently introduced nasal corticosteroids have a substantially reduced systemic bioavailability profile and as such negate this concern. Furthermore, in children and asthmatic patients requiring inhaled corticosteroids, careful selection of the intranasal corticosteroid in conjunction with their use at the lowest possible doses, will significantly reduce the potential for any systemic effects.[176,179]

The current consensus of opinion, as has been expressed in the recent ARIA document,[5] recommends topical antihistamine therapy for mild persistent organ-limited disease or as an on-demand medication for intermittent disease. Intranasal corticosteroids are now accepted as the gold standard therapeutic choice in allergic rhinitis,[250] and as such are recommended as highly effective first-line treatment for patients with allergic rhinitis with moderate-to-severe and/or persistent symptoms (figure 1).[5,105-107,112] In practice, however, the balance between the two agents should be tailored to the individual needs of the patient. There is no evidence that combining intranasal corticosteroids and intranasal antihistamines provides any additional therapeutic benefit to intranasal corticosteroids alone.[112,126] Furthermore, the recent intriguing evidence that 'as required' treatment with an intranasal corticosteroid is more effective than 'as required' oral antihistamines, has yet to be confirmed and assimilated into mainstream practice.[251]

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Erratum

Vol. 26, No. 1, 2003

Pages 13-14: The last sentence of the third paragraph of the article should read:
'Rosuvastatin is 90% excreted in the faeces as unchanged drug via active transport pathways in the liver.[2] The small amount of rosuvastatin that is metabolised (<10%) is done so via CYP2C9 and CYP2C19.[3]'
Page 14: the entry for rosuvastatin in the right-hand column of table I should read: *'Biliary clearance'*
Page 20: An additional reference is to be inserted between the current references 2 and 3, which becomes the new reference 3:
Martin P, Dane A, Schneck D, et al. Disposition of new HMG CoA reductase inhibitors ZD4522 following dosing in healthy subjects [abstract]. J Clin Pharmacol 2000; 40: 1056
[Martin J, Krum H. Cytochrome P450 Drug Interactions Within the HMG-CoA Reductase Inhibitor Class. Drug Safety 2003; 26 (1): 13-21]

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: 4912
LULLA *et al.*	Art Unit: 1616
Appl. No. 10/518,016	Examiner: Nielsen, Thor B.
Filed: July 6, 2005	Atty. Docket: PAC/20632 US (4137-04700)
For: **Combination Of Azelastine and Steroids**	

Declaration of Dr. Sujeet Rajan Under 37 C.F.R. § 1.132

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

Sir:

1. I, Dr. Sujeet Rajan (MD, DETRD, DNB), hereby declare and state as follows:

2. I am currently a paid consultant for Cipla. I am not being compensated for the services related to this Declaration. I am not a shareholder of Cipla. I do not have any other financial interest in the allowance or issuance of the above-captioned patent application.

3. I hold the degree of MD, DETRD, DNB. A recent copy of my Curriculum Vitae, accurately listing my scientific credentials and work experience, is attached herewith as Exhibit A.

4. As stated in by Curriculum Vitae, I am a Consultant Chest Physician at **Bombay Hospital Institute of Medical Sciences** (Since August 2000); Honorary Consultant Chest Physician – **Bhatia Hospital** (Since February 1996), (Asst. Honorary Chest Physician – 1995-1996); and Honorary Chest Physician & Bronchoscopist – **Motiben Dalvi Hospital & ICU** (Since March 1997). I am a ***Member*** of the following Societies-

Indian Chest Society (Life Member); American College of Chest Physicians (ACCP). I am on the ***Editorial Advisory Board*** of the following journals: Indian Practitioner, and Indian Diet and Nutrition. I am also a reviewer of the *Journal of Association of Physicians of India (JAPI)*. As evidenced in my Curriculum Vitae, I have extensive experience in the treatment of respiratory tract diseases.

5. Based on my education and experience, I am knowledgeable about allergic rhinitis and non-allergic vasomotor rhinitis.

6. It is my understanding that the claims in the above-captioned patent application recite a pharmaceutical composition comprising azelastine or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, and a pharmaceutically acceptable ester of fluticasone wherein the pharmaceutical formulation is in a dosage form suitable for nasal administration (the "claimed composition").

7. For at least the reasons discussed herein, it is my opinion that the claimed composition represents the fulfillment of a long-felt, but previously unmet, need by patients and healthcare practitioners for management of symptoms of allergic rhinitis and non-allergic vasomotor rhinitis.

8. Duonase®, a nasal spray product developed by Cipla which contains azelastine hydrochloride and fluticasone propionate, is an embodiment of the claimed composition commercially available in India.

9. Over 50 % of our asthma patients have allergic rhinitis (AR). Prior to Duonase® being introduced in India, we have traditionally used nasal corticosteroids alone in treating our patients for both AR and non-allergic vasomotor rhinitis.

10. Though nasal steroids are an effective medication for AR, their time to onset for action is a bit prolonged, and therefore their use *alone* has been associated with poorer adherence rates in my practice, and subsequently lead to the excess and misuse of over the counter decongestants, which is harmful. The dangers of short-term use of decongestants are well known to the medical community worldwide. Also, use of nasal steroids alone typically required a treatment period of 4 to 8 weeks or longer, which is unpopular with patients and has lead to failure to complete the treatment regimen. Accordingly, long-term problems have existed with use of nasal steroids alone.

11. Another medicine that is typically prescribed for AR is oral anti-histamines. However, the use of *oral* anti-histamine is associated with some common side effects such as sedation, cognition difficulties, dryness of the mouth, and significantly troublesome lower urinary tract symptoms (LUTS) in elderly patients with benign prostatic enlargement. Accordingly, long-term problems have existed with use of oral anti-histamines.

12. Nasal corticosteroids in conjunction with oral antihistamines have also been prescribed for AR, but are characterized by delayed effects with significant potential side effects such as sedation, cognition difficulties, dryness of the mouth, and significantly troublesome lower urinary tract symptoms (LUTS) in elderly patients with benign prostatic enlargement. Accordingly, use of nasal corticosteroids in conjunction with oral antihistamines for treatment of AR is both unremarkable and undesirable.

13. Duonase® solves many of these long term problems. Duonase® provides superior and almost immediate relief from symptoms of AR, so much so that our patient's compliance and adherence with treatment improves considerably. Improved compliance and adherence ensures that my patients not only get fluticasone with the fast-acting azelastine,

but continue to take it for periods ranging from 2 weeks to 2 months. Furthermore, I have observed that with the use of Duonase® the side effects which are encountered with oral anti histamine are surmounted. Duonase® has also substantially reduced both our prescription, and the patients' use, of decongestants, and their subsequent rebound congestant effects. Duonase® use has obviated the need for topical decongestants in our practice. Accordingly, in comparison to traditional treatments, the number of medications comes down, the rhinitis is now better controlled, and the patient is maintained on anti-inflammatories more consistently through use of Duonase®.

14. For patients with moderate to severe intermittent rhinitis, Duonase® is the treatment of choice. Duonase® serves as an excellent short-term treatment (lasting 10 to 14 days) to bring all symptoms of AR quickly under control, with minimal side effects, and with an increased efficacy over mono-therapy treatments. Future episodes of moderate to severe symptoms, even in a patient with intermittent AR, when the patient is travelling and especially when primary care physician is not accessible, would tremendously benefit with a short 10-14 days course of nasal corticosteroids and antihistamine combination provided by Duonase®. This could therefore be prescribed as an action plan, just as "prednisolone rescue courses" are in asthma. All in all, Duonase® is an indispensable part of our therapeutic armamentarium in the treatment of both AR and non-allergic vasomotor rhinitis.

15. In summary, it is my opinion that the claimed composition represents the fulfillment of a long-felt, but previously unmet, need by patients and healthcare practitioners for management of symptoms of AR and non-allergic vasomotor rhinitis via its superior efficacy, improved compliance and adherence with treatment, faster response time, and reduced side effects.

16. I further state that all statements made on my own knowledge are true and that all statements made on information and belief are believed to be true and further that willful false statements and the like are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the U.S. Code and may jeopardize the validity of the application or any patent issuing thereon.

16/AUG/2011
Date

Dr. Sujeet Rajan (MD, DETRD, DNB)

Dr. SUJEET K. RAJAN
MD (Chest) DNB (Resp. Med.)
Reg. No. 66905
Consultant Chest Physician
Bombay Hospital

132091 v1/04137.04700

Exhibit A

RESUME

Name	:	Sujeet K. Rajan
Nationality	:	Indian
Address	:	Residence: 503 Aashiana, 3, Gunpowder Lane No.2, Mazgaon, Mumbai 400 010. Tel no. 91-22- 2378 1754 Mobile: 91 - 98201 91302 E-Mail: skrajan@hotmail.com Clinics: Bhatia Hospital Basement Clinic Mumbai 400 007 Tel: 91-22-66660020-22 Bombay Hospital 2nd Floor, New Wing Room no. 6 New Marine Lines Mumbai – 400 020 Tel: 22090227
Date of Birth	:	30-06-1967
Marital Status	:	Married
Qualifications	:	*MD: (Chest Medicine & TB)* *DETRD: (Diploma in Environmental, Tuberculosis & Respiratory Disease)* *DNB: (Respiratory Medicine)*
Present Occupation & Affiliations	:	Consultant Chest Physician – **Bombay Hospital Institute of Medical Sciences** (Since August 2000) Honorary Consultant Chest Physician – **Bhatia Hospital** (Since February 1996) (Asst. Honorary Chest Physician – 1995-1996) Honorary Chest Physician & Bronchoscopist - Motiben Dalvi Hospital & ICU (Since March 1997) ***Member*** - Indian Chest Society (Life Member) American College of Chest Physicians (ACCP) ***Editorial Advisory Board***: Indian Practitioner, Indian Diet and Nutrition ***Reviewer –*** *Journal of Association of Physicians of India (JAPI)*

ACADEMIC QUALIFICATIONS:

Name of School/ College	Board/Univ.	Year of Passing	Attempts	Degree/ Diploma
Seth G.S. Medical College	National Board of Exams	February 1994	1	*D.N.B. (Respiratory Diseases)
Seth G.S. Medical College	Univ. of Bombay	January 1994	1	M.D. (TB and Chest)
Seth G.S. Medical College	College of Physicians and Surgeons	1993	1	*DETRD
Grant Medical College	Univ. of Bombay	1989	1	IIIrd MBBS
Grant Medical College	Univ. of Bombay	1988	1	IInd MBBS
Grant Medical College	Univ. of Bombay	1986	1	Ist MBBS
St.Xavier's College, Bombay	Maharashtra	1985	1	HSC (1st with Distinction)
Activity High School, Bombay	ICSE, New Delhi	1983	1	ICSE (1st Class)

* Diploma in Environmental, Tuberculosis & Respiratory Diseases
* Diplomate of the National Board

ACADEMIC SCHOLARSHIPS AND AWARDS

◊ Secured prizes at an Inter-collegiate Essay Competition on Environmental Pollution during Junior College.

◊ Received merit certificates for standing 1st in Microbiology and IInd overall at the IInd MBBS Examination at Grant Medical College.

WORK EXPERIENCE

Pre-M.D.

◊ Completed post-examination (MBBS) Internship training for a period of one year. Of this, 2 months were in Internal Medicine; 2 months in General Surgery; 2 months in Obstetrics and Gynaecology and 6 months of Rural Training.

During The Period of Registration for M.D.

Junior Resident in Chest Medicine: (1 year)

◊ Gained wide experience in the management of both outdoor and indoor patients admitted to the Chest Unit of the KEM Hospital. Worked in the Intensive Respiratory Care Unit of the KEM Hospital and acquired extensive skill in the management of patients in respiratory failure requiring assisted ventilation with respirators. Seen and managed a number of cases of Adult Respiratory Distress Syndrome (ARDS), fulminant pneumonia and neuromuscular disorders requiring ventilatory support. Acquired expertise at central venous canulation, venesection, arterial canulation, endotracheal intubation, percutaneous lung biopsies, trocar and canula drainage of pneumothorax, pleural aspirations and pleural biopsies (both visceral as well as parietal). Also assisted in fibreoptic bronchoscopy and interventional procedures through the bronchoscope.

◊ Was a member of the Support Faculty of the Continuing Medical Education (CME) programme of the Royal College of Physicians (Edinburgh) and Indian College of Physicians held at Seth G.S. Medical College.

Residency in Internal Medicine: (6 months)

◊ During this period got acquainted with management of both outdoor and indoor (both routine and emergency) medical patients. Gained expertise in ascitic fluid aspirations, lumbar puncture technique for CSF analysis and venesection. Also became adept at liver and kidney biopsies.

Residency in Cardiology: (3 months)

◊ Gained adequate experience in the management of patients admitted to the 20-bed Intensive Coronary Care Unit of the KEM Hospital. This included cases of congestive cardiac failure, infective endocarditis, ischaemic heart disease, congenital heart disease and patients admitted for observation following cardiac catheterization. Passed an adequate number of transvenous cardiac pacemaker wires and gained expertise at insertion and wedging of pulmonary artery wedge pressure (Swan-Ganz) catheters.

Registrar in Chest Medicine: (1 year)

◊ Was independently in charge of the Out-patient Department (OPD) of Chest Medicine and managed patients with bronchial asthma, pulmonary tuberculosis, bronchiectasis and lung malignancies on an OPD basis. Was also independently in charge of the 25-bed Chest Medicine ward where expertise in the indoor management of various lung disorders such as chronic obstructive airway disease, bronchial asthma, interstitial lung diseases and pleural, mediastinal and diaphragmatic disorders was attained.

◊ Acquired expertise in the performance and interpretation of pulmonary function tests and pulmonary exercise stress testing.

◊ Acquired competence in fibreoptic bronchoscopy and interventional procedures through the bronchoscope such as bronchoalveolar lavage, transbronchial lung biopsies and direct mass biopsies.

◊ Attended a number of thoracic surgeries and followed the patients closely in their post-operative period.

◊ Attended and assisted in various interventional radiological procedures such as bronchial artery embolisation, bronchography, fine needle aspiration biopsy of lung / mediastinal masses under fluoroscopy and computed tomographic (CT) guidance.

◊ Performed several allergy tests.

◊ Attended postgraduate classes, seminars and clinical meetings conducted by the Department of Chest Medicine at the KEM Hospital regularly. Actively participated in a number of case presentations and clinical discussions and regularly involved in undergraduate teaching. Attended a series of lectures in Occupational & Environmental diseases held by the College of Physicians and Surgeons, Bombay at the Central Labour Institute, Bombay. Secured a Diploma in the same in October 1993.

◊ Submitted a dissertation on "High-Resolution Computed Tomography in Chronic Infiltrative Lung Disease" for the M.D. Examination in January 1994.

Lecturer in Chest Medicine (5 1/2 months)

◊ Took an active part in post-graduate teaching. Conducted a teaching and decision-making round in the chest medicine ward twice a week.

◊ Assisted in conducting teaching programmes in the Chest Medicine Unit.

◊ Played a supervisory role in the management of the Pulmonary Function and Blood Gas Laboratory at the Dept. of Chest Medicine in KEM Hospital.

◊ Presented a paper on "Pefloxacin in the Treatment of Nosocomial Respiratory Tract Infections" at the XIIIth National Congress of Respiratory Diseases held in Madras in January 1994.

◊ Participated and lectured at a Workshop on Physiotherapy and Rehabilitation held by the Dept. of Chest Medicine at the KEM Hospital.

POST M.D. - KEM Hospital (January - October 1994)

◊ Was independently in charge of fibreoptic bronchoscopy and acquired expertise in the same, including interventional procedures through the fibreoptic bronchoscope.

◊ Actively involved in post-graduate and undergraduate teaching.
◊ Gained extensive experience in the management of the critically ill patients as well as maintenance of equipment in the Intensive Respiratory Care Unit.

◊ Actively involved in a project conducted by the Environmental Pollution Research Centre in the critically polluted area of Chembur, Bombay.

◊ Presented papers on

(i) Role of high resolution CT scan in chronic infiltrative lung disease and
(ii) Azithromycin in lower respiratory tract infections
at XIV National Congress on Respiratory Diseases held in Pune in December 1994

Mathadi Trust Hospital (Since November 1994)

◊ Independently in charge of Respiratory Medicine OPD once a week on Tuesdays.

Bhatia General Hospital (Since January 1996)

◊ Independently looking after patients with respiratory diseases in the ward (250-bedded hospital) as well as critically ill patients with respiratory problems in the Intensive Care Unit.

BEST Undertaking - Medical Department (June - December 1996)

◊ Consultant Chest Physician in charge of the Respiratory Medicine OPD

Smt. Motiben Dalvi Hospital (since March 1997)

◊ Honorary Bronchoscopist and conducting a Respiratory clinic once a week on Wednesdays. Also attending cases at this 75-bedded hospital and intensive care unit.

LECTURES DELIVERED

International Level

1. COPD Management: Beyond bronchodilators. Respiratory Disease Study Group (RDSG) Annual Conference, Colombo, Srilanka, 4th November, 2006.

2. Non-invasive ventilation: Practical aspects. RDSG Annual Conference, Colombo, Srilanka, 4th November, 2006.

3. "Management of Paediatric Asthma and Workshop on Inhaled Devices," National Conference of Paediatric Association of Tanzania, Dar-es-salaam, Tanzania, 28th April, 2006.

4. "Managing COPD in clinical practice," Dar-es-salaam, Tanzania, 17th March, 2006.

5. "Modern day management of Asthma, Dar-es-salaam, Tanzania, 16th March, 2006.

6. "Differentiating asthma from COPD and managing Paediatric Asthma" - 30th January, 2005. Respiratory Update Symposium, Ajman, United Arab Emirates.

7. "Newer Management strategies in Asthma" – 26th January, 2005. Al – Makhtom Medical College, Dubai, United Arab Emirates.

8. "Management of COPD and use of various inhaler devices for airway disease," Physicians Association of Myanmar, Yangon, Myanmar, 3rd October, 2004.

9. "COPD – Issues in Primary Care," International Union against tuberculosis and lung disease (IUATLD) Conference, Europe Region, Moscow, Russia, 25th June, 2004

10. "Diagnosis and Management of Pediatric Asthma," Association of Physicians of Nepal, Katmandu, Nepal, 22nd May, 2004.

11. "Diagnosis and Management of Obstructive Sleep Apnoea," Taj Samudra, Citihealth Conference, Columbo, Sri Lanka, 24th January, 2004.

12. "Differentiating Asthma from COPD," Physicians Association of Galle, Galle, Sri Lanka, 22nd January, 2004.

13. "Modern day management of Asthma and COPD," Arab Health Conference, Dubai, UAE, 18 and 19th January, 2004.

14. "Managing Obstructive Airway Disease in Practice," Association of Physicians of La Paz, La Paz, Bolivia, 22nd August, 2003.

15. "Differentiating Asthma from COPD," Association of Physicians of Santacruz, Santacruz, Bolivia, 21st August, 2003.

16. "Management of Acute Severe Asthma," Department of Medicine, Lima Medical School, Lima, Peru, 19th August, 2003.

17. "Inhalation Devices for Asthma and COPD," Workshop at the 10th CPA Conference, Ocho Rios, Jamaica, 16th August, 2003.

18. "COPD – Is it really irreversible?," 10th CPA Conference, Ocho Rios, Jamaica, 15th August, 2003.

19. "Series of lectures on asthma, COPD, pulmonary manifestations of HIV and anti-retroviral therapy," 2nd National Conference on HIV, HBV and HCV infections, Muscat, Sultanate of Oman, 27th – 30th April 2003.

20. "Series of lectures on asthma, COPD and pulmonary manifestations of HIV disease," Kenya Association of Physicians treating lung disease (KAPTLD), Nairobi, Kenya, 19th March 2003 – 21st March 2003

21. "Panel discussion on asthma management - First Annual conference on respiratory diseases," Colombo, Sri Lanka 17th November 2002

22. "Management of obstructive airway disease – Newer Concepts," Association of Physicians of Baghdad, Iraq, 15th July 2002.

23. "Series of lectures on Asthma, COPD and Community acquired pneumonia"; in Jamaica. These lectures supported by America Jamaica Health Foundation and held at Kingston, Savlamar, Montego Bay and Ocho Rios.

24. "What patients should understand about Asthma," Lecture to Women's Federation of Iraq, Baghdad 20th November 2001.

25. "Asthma – An overview" Association of physicians of Iraq, Baghdad 19th April 2001.

26. "Acute Respiratory Failure" National Conference of Physicians of Tanzania, Dar-es-salaam, 30th March 2001.

22. "Asthma Management in India – Current Concepts and Future Advances"
    - Muscat General Practitioners Association, Muscat, Sultanate of Oman, 5th March 2000.

National Level

1. MDR-TB: What's new? Chest Summit, New Dehli, 14th October.

2. Adherence Issues in Asthma and COPD, Kanpur, 26th July.

3. COPD workshop (Evidence translated in Practice) – ACCP certified workshop, Jaipur, 8th – 9th June, 2006.

4. COPD workshop (Evidence translated in Practice) – ACCP certified workshop, Lonavla, 3rd – 4th June, 2006.

5. COPD: Beyond bronchodilaton, Lucknow CME on Respiratory and Critical Care Medicine, 26th February, 2006.

6. COPD workshop (Evidence translated in Practice) – ACCP certified workshop, Vizag, 4th – 5th February, 2006.

7. Hypersensitivity Pneumonitis – National Conference of the Indian Chest Society (NAPCON), Kolkata, 19th November, 2005.

8. Complete Polysomnography is not required for diagnosis of sleep apnoea. Sleep Apnoea Diagnosis Debate. NESSCON, Mumbai. 6th November, 2005.

9. Beta-agonists in asthma: Rescue, control and remodeling. National Allergy Conference (ICCAICON) Jaipur, 17th October, 2005.

10. COPD: Putting guidelines into practice. Rajasthan APICON Conference, Jodhpur, 15th October, 2005.

11. Chemotherapy of Tuberculosis. National Infectious Disease Update, PD Hinduja Hospital, 26th August, 2005.

12. Differentiating asthma from COPD. COPD Update. 6th August, 2005, Bhubaneshwar.

13. Obstructive Sleep Apnoea – Basic Principles. Nasik IMA, Meeting, 21st July, 2005, Nashik.

14. Understanding and treating obstructive sleep apnoea, Valsad IMA meeting, Valsad, Gujarat.

15. COPD Today: Easier to understand; easier to manage. 28th May, 2005, Bangalore – IMA meeting.

16. Workshop on Asthma and COPD, 23rd , 24th April 2005, Coimbatore.

17. Out patient management of COPD, 20th February 2005.

18. Pre-operative evaluation in lung surgery. 19th February 2005. ICMAP Conference, Mumbai.

19. COPD Today: Easier to understand; easier to manage. 22nd January, 2005. Annual Physicians of India Conference (APICON), Mumbai.

20. COPD and Asthma: Issues in Primary Care. Bikaner Annual Asthma Update, 9th January 2005.

21. "The Role of anticholinergics in Asthma," Indian Congress of Allergy, Immunology and Asthma, Bhubaneshwar, Orissa, 19th December, 2004.

22. "COPD and Asthma, similarities and differences," 10th Conference of the Transpacific Society of Allergy and Immunology, 22nd November, 2004.

23. "The link between sinusitis and asthma," 9th Asian Research Symposium on Rhinology, Hotel Hilton Towers, 19th November, 2004.

24. "COPD: Easier to understand, easier to manage," Rajasthan APICON, 30th October, 2004.

25. "COPD issues in primary care," Indian Chest Society – Eastern Region Conference, Guwahati, 1st August, 2004.

26. "Recent Advances in the Management of COPD," IMA Meeting, Srinagar, Jammu and Kashmir, 3rd July, 2004.

27. "COPD: Easier to understand, easier to manage," IMA Meeting, Amritsar, 20th February, 2004.

28. "Diagnosis and Management of Allergic Rhinitis," National TB Conference, Hotel Regent, Mumbai, 3rd January, 2004.

29. "Diagnosis and Newer Management Strategies for COPD." Goa IMA Symposium, Goa 9th August, 2003.

30. "An Overview of the Management of COPD" Cipla Symposium on COPD, Bhubaneshwar, Orissa, 15th June 2003.

31. "COPD Management and the Role of Tiotropium Bromide" Cipla Symposium on COPD, Lucknow, 11th May 2003.

32. "Why asthma is good for your practice" IMA Bardoli meeting, Bardoli, Gujarat, 9th March 2003.

33. "Difficult Asthma" Jamshedpur IMA Association. 4th January 2003

34. "The role of leukotriene modifiers in management of asthma." Cipla symposium, Jodhpur, Rajasthan, 21st December, 2002

35. "Diagnosis and Management of pneumonia," Bhubaneshwar IMA meeting, 16th December 2001.

36. "Managing Asthma in General Practice," Jalgaon, IMA, 22nd August 2001.

37. "Long term Management of Bronchial Asthma" Ambejogai Medical College, Symposium on HIV and Asthma, 4th March 2001.

38. "Out Patient Management of COPD" Symposium on Management of COPD, Chennai 17th February, 2001.

39. "Long term Management of Bronchial Asthma" Ambejogai Medical College, Symposium on HIV and Asthma, 4th March 2001.

40. "Modern-day management of Asthma" KSVS IMA Lecture, Sawantwadi 24th September, 2000

41. "Management of Community-acquired pneumonias" Surat IMA meeting

42. "Management of Asthma in clinical practice, Rajkot and Bhavnagar IMA meetings 24th and 25th June, 2000

43. "Current Day Management of Asthma"
Lecture at IMA Yeotmal Meeting, Yeotmal, 13th February 2000.

38."Asthma Management at the Turn of the Millennium"
75th Jubilee Conference of the Indian Medical Association (PLATICON), Pune, 29th December 1999.

39. "Advances in Asthma Management"
Family Physicians' Association of Nashik, 11th December, 1999.

40. "Management of Occupational Asthma"
Update on Occupational Respiratory Disorders, Gharda Chemicals, Chiplun, Mahad, 26th Sept. 1999.

41. "Asthma Management at the Turn of the Millennium
Daman Medical Association, 12th Sept. 1999.

42. "Modern-Day Management of Asthma, Cipla Symposium on Asthma, Ranchi, 4th September 1999.

43. "Diagnosis and Management of COPD"
    - Miraj-Sangli Medical Association, 25th July, 1999.

44. "Modern Day Management of Asthma"

- Cipla Symposium on Asthma, Lucknow, 18th July, 1999.

45. "Asthma Management"
    - Dahanu Medical Association, 30th May, 1999.

46. "Modern Day Management of Asthma"
    - Cipla Symposium on Asthma, Cochin, 23rd May, 1999.

47. "Pulmonary Medicine at the Turn of the Millennium
    - Vapi Medical Association, 11th April, 1999.

48. "Aerosol Delivery Systems in Asthma"
    Twin-city Symposia on Asthma: Symptom Relief to Disease Control. Co-lectured with Professor Eric. D. Bateman, (South Africa) – Pune, 9th March, 1999, Calcutta, 11th March, 1999.

49. "The Role of Corticosteroids in Asthma Management"
    Annual Conference of the National College of Chest Physicians, Udaipur, 30th January 1999.

Local Level

1. "Steroids in Pulmonary Disease, Malad Medical Association, Mumbai, 21st May, 2006.

2. "HIV & Tuberculosis, Bombay Medical Congress, Mumbai, 12th February, 2006.

3. "Outpatient management of bronchial asthma and early COPD"
    - 'A' Ward Medical Association - August 1996

4. "Management of multi-drug resistant tuberculosis"
    - Mahim-Dharavi General Practitioners' Association - December 1996

5. "Usage of different inhalation devices in the management of asthma"
    - Ghatkopar General Practitioners' Association - February 1996

6. "Indications and types of Mechanical Ventilation"
    - Workshop on Mechanical Ventilation at Bhatia General Hospital - July 1996

7. "Guidelines for Management of Bronchial Asthma in children and adults"
    - INHS Ashvini Hospital, Paediatric Dept, June 1996

8. Series of lectures on Respiratory Medicine at the IMA (Indian Medical Association)
    - Undergraduate teaching programme

9. "Management of Bronchial Asthma"
    - Nair Hospital Pharmacology Symposium - September 1996

10. "Recent Advances in Asthma Management"
    - Symposium on Asthma and Air Pollution at the BEST - 27th April 1997

11. "Recent Advances and Newer Guidelines in Asthma Management"
    - Symposium on Asthma Management in Adults and Children, Dombivli Chapter of IMA, Dombivli - 29th June 1997

12. "Inhalation Therapy in Bronchial Asthma and COPD"
    - Internship Orientation Programme, Grant Medical College - 21st July 1997

13. "Newer Guidelines for the Management of Asthma in Children"
    - Symposium on Paediatric Asthma, Dept of Paediatrics, Grant Medical College & J J Group of Hospitals - 29th July 1997
14. "Why Prevent Asthma?"
    - Symposium on Preventive Management of Asthma, 24th December 1997

15. "Aerosol Delivery Systems for Asthma and COPD"
    - Annual Conference on Allergy, Asthma and Applied Immunology, HN Hospital, Mumbai, 26th December, 1998.

16. "Basic Issues in the Management of COPD,
    - Annual Update of Railway Hospital Medical Association, Jagjivan Ram Hospital, 27th July, 1995.

17. "Management of Community Acquired Pneumonias"
    - Santacruz Medical Association, Glenmark Symposium on Respiratory Infections, 30th September, 1999.
18. "Management of Pneumonias"
    - A-Ward Medical Associations Meeting 17th October, 1999.

19. "Modern-Day Management of Asthma"
    - Mahim-Dharavi G.P. Association, Tata Auditorium 24th October, 1999.

20. "Community-Acquired Pneumonias and The Role of Macrolides"
    - KEM Hospital Chest Dept. 27th October, 1999.

21. "Recent Advances in Asthma Management"
    - Annual Update in Medicine, INHS Ashwini Hospital, 9th January, 2000.

22. " Asthma Management and Yoga"
    - Yoga Vidya Niketan, 15th January 2000.

23. " Current Concepts in Tuberculosis and Pneumonia"
    - Chest Radiology Meet of the Radiology Education Foundation – Tata Memorial Hospital, 28th and 29th January 2000.

24. "Recent Advances in Asthma Management"
    - Annual Update on HIV, TB and Asthma Management, Tata Memorial Hospital, 18th March 2000.

23. "Recent Advances in the Management of COPD"
    - Surgical Society of Thane, Thane, 23rd April 2000.

24. "Long Term Management of Adult Asthma"

- Kalyan IMA Meeting, Kalyan, 21st May 2000.

24. "Modern day management of Asthma" Bhandup Medicos, 21st July 2000

25. "Nebuliser usage in Clinical Practice", Bombay Hospital Physiotherapy Department 4th August 2000

26. "Drugs and Delivery Systems for Asthma" Department of Pharmacology, J. J. Hospital and Grand Medical College, 7th August 2000

27. "Preventive Therapy in Asthma Management". Prince Aly Khan Hospital Mumbai 4th November 2000

28. "Differentiating asthma from COPD. Mid-down Medicos Association," Mumbai, 19th November 2000

29. "Pulmonary manifestations of HIV" Cipla Symposium on HIV, Bhatia General Hospital, Mumbai 18th June 2001.

30. "Community acquired infections of the lung," K. J. Somaiya Hospital, Mumbai 17th August 2001.

31. "Advanced Combination Therapy in Asthma," Malad, General Practitioner's Association, 3rd November 2001.
32. "Care and Maintenance of a Fibre Optic Bronchoscope," Workshop at the National Conference of Chest Diseases, Mumbai 7th November 2001.

33. "New Fluoroquinolones in community acquired pneumonia," Major Symposium on Lung infection at National Conference of Chest Diseases, Mumbai 9th November 2001.

34. "Panel Discussion on community acquired pneumonias," Asia Pacific Congress on Chest Diseases," Mumbai 1st December 2001.

35. "Managing COPD in General Practice," INCHES (GP Association), Bhatia General Hospital, Mumbai 27th December 2001.

36. "Management of Asthma and the relevance of spirometry to general practitioners", Inches GP association 26th May 2002

37. "Managing tuberculosis in private practice – Advantages and disadvantages of DOTS." - Haffkine Institute, Mumbai. 10th August 2002

38. "Differentiating asthma from COPD and the need for spirometry in general practice," A Ward Medical Association. 8th September 2002

39. "Why asthma is good for your practice" Lecture at Annual Conference of the GPA, Mumbai, 28th December 2002

40. "Difficult Asthma" Lecture at IMA Annual Conference, Mumbai, 18th January 2003

41. "Use and interpretation of lung function test" North-West Mumbai Association of Anaesthetists 15th February 2003

42. "Outpatient Management of asthma for Nurses," Workshop for Diagnosis and Management of Asthma for Nurses. 26th June, 2005. LH Hiranandani Hospital, Powai, Mumbai.

43. "Obstructive Sleep Apnoea" – What the general practitioner must know. 'A' Ward Medical Association monthly CME, Mumbai, 13th November, 2005.

Papers and Articles Published

1. Complications and Sequelae of Pulmonary Tuberculosis. Mahashur A A & **Rajan S**. Integral Physician's Digest. TB Issue Vol.1. No.1, January 1994

2. Newer Guidelines and their Role in Asthma Management. **Rajan S** - The Journal of General Medicine Vol. 9, No.2, 1997, p 11-18

3. Inhalation Devices and Inhalational Therapy in Asthma. Joshi SR & **Rajan S** The Journal of General Medicine Vol. 9, No. 2, 1997, p 19 - 30

4. Newer Guidelines and Management Strategies for Young Children with Asthma. **Rajan S.** Paediatric Pulmonary Update Vol. 9, No.3, September 1997 p 17-21

5. Asthma Guidelines, **Rajan S** Letters to the Editor, Thorax 1997; 52: 932

6. Inhaled fluticasone in the management of asthma. **Rajan S,** Mahashur A A, Mathur U S, poster presentation at the 8th European Respiratory Congress, September 22, 1998, Geneva, Switzerland.

7. Diagnosing Asthma in general practice. **Rajan S**. The Indian Practitioner Vol. 54, No. 6, June 2001.

8. Salmeterol/fluticasone combination product (SFC) provides better asthma control compared to high dose fluticasone (FP) in symptomatic patients with asthma. Joshi J, Jagannath K, Chhabra S, **Rajan S** et al. Poster at ERS Congress, September 2005.

9. Assessment of usability of a multi-dose dry powder inhaler (multi-haler) in healthy volunteers and mild asthmatic- P. 567 poster presented at the European Respiratory Society meeting at Stockholm, 2007.

10. Pneumonia Chapter in API Textbook of Medicine. Vol-1, Chapter-8, Section 7, Pgs.368-373-2008.

11. Strategies to prevent COPD exacerbations Pg. 835-843 part II Medicine update, Association of Physicians of India 2009.

International Conferences Attended

- Vth European Respiratory Society Congress September 16-20, 1995, Barcelona, Spain
- VIIth European Respiratory Society Congress September 20-24, 1997, Berlin, Germany
- VIIIth European Respiratory Society Congress September 19-23, 1998, Geneva, Switzerland
- IXth European Respiratory Society Congress October 9-13, 1999, Madrid, Spain
- World Congress on Lung Health, August 30 –September 3 2000, Florence, Italy
- Asia Pacific Congress on Chest Diseases, November 29 – December 2, 2001, Mumbai, India
- XIIth European Respiratory Society Congress September 14 - 18, 2002, Stockholm, Sweden
- Workshop on Sleep - Disordered Breathing and Non –Invasive Ventilation, Syndey, Australia October 14 – 25, 2002
- Commonwealth Pharmaceutical Association Congress August 14 - 17, 2003, Ocho Rios, Jamaica
- 13th European Respiratory Society Meeting, Vienna, Austria, September 2003.
- National Congress of Respiratory Disease, St. Petersburg, Russia, November 2003.
- IUATLD (Europe Region Meeting) Moscow, Russia, 23rd to 26th June 2004.
- 14th European Respiratory Society Meeting, Glasgow, Scotland, UK, 4th to 8th September 2004.
- Clinical Observer: Royal Brompton Hospital. Interstitial Lung Disease Unit, London, UK. 7th September 2005 to 15th September, 2005.
- European Respiratory Society Meeting, Copenhagen, Denmark. 17th September – 21st September 2005.
- European Respiratory Society Meeting, Miinich, Germany,2nd -6th September ,2006.

Conferences organized

Organizing committee – National Association of Pulmonologists Congress (NAPCON), November 2001, Mumbai.

Organizing Secretary (Workshops) – 10th Conference of the Transpacific Society of Allergy and Immunology, Hilton Towers, Mumbai, 21st to 23rd November, 2004.

Core Committee Member: ROAD (Refresher Course on Obstructive Airway Disease) at Chest Research Foundation, Pune.

Languages Known : English, Hindi, Marathi, Malayalam and German.

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	Thor B. Nielsen
Attorney Docket Number	PAC/20632 US (4137-04700)

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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	Thor B. Nielsen
	Attorney Docket Number	PAC/20632 US (4137-04700)

	1	SALIB RAMI JEAN, et al., "Safety and Tolerability Profiles of Intranasal Antihistamines and Intranasal Corticosteroids in the Treatment of Allergic Rhinitis," Drug Safety 2003, Vol. 26, No. 12, Cover page, publication page, pgs. 863-893, ADIS Data Information BV.	☐
	2	SIMPSON, RICHARD J., "Budesonide and terfenadine, separately and in combination, in the treatment of hay fever," Annals of Allergy, December, 1994, Vol. 73, Cover page, publication page, pgs. 497-502.	☐
	3	JUNIPER, E F., et al., "Comparison of beclomethasone dipropionate aqueous nasal spray, astemizone, and the combination in the prophylactic treatment of ragweed pollen-induced rhinoconjunctivitis," Journal of Allergy and Clinical Immunology, March 1989, Vol 83, No. 3, Cover page, Publications page, pgs. 627-633, American Academy of Allergy and Immunology, C.V. Mosby Co.	☐
	4	BARNES, M. L., et al., "Effects of levocetirizine as add-on therapy to fluticasone in seasonal allergic rhinitis," Clinical and Experimental Allergy, January 27, 2006, Vol. 36, pgs. 676-684, Blackwell Publishing Ltd.	☐
	5	Applicants response to foreign communication - EP 03738280.1 (EP Patent 1519731) , September 6, 2010, 15 pages.	☐
	6	File history of Australian Patent Application No. AU2003244799, 38 pages.	☐
	7	File history of Brazilian Patent Application No. PI 0312128-3, 27 pages.	☐
	8	File history of Canadian Patent Application No. 2,489,427, 19 pages.	☐
	9	File history of Korean Patent Application No. 10-2004-7020819, 89 pages.	☐
	10	File history of Mexican Patent Application No. PA/a/2004/01266 (now Patent No. 265349), 86 pages.	☐
	11	File history of Polish Patent Application No. P-373001, 95 pages.	☐

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	Filing Date	2005-07-06
	First Named Inventor	Amar Lulla
	Art Unit	1616
	Examiner Name	Thor B. Nielsen
	Attorney Docket Number	PAC/20632 US (4137-04700)

	12	File history of Russian Patent Application No. RU 2361593 C2, 65 pages.	☐
	13	File history of South African Patent Application No. 2005/0331 (now Patent No. 2005/0331), 18 pages.	☐
	14	Applicants response to foreign communication - CA 2489427, December 20, 2010, 10 pages.	☐

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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.

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	First Named Inventor	Amar Lulla
	Art Unit	1616
	Examiner Name	Thor B. Nielsen
	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)	2011-08-16
Name/Print	Rodney B. Carroll	Registration Number	39,624

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EFS ID:	10740483
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
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Receipt Date:	16-AUG-2011
Filing Date:	06-JUL-2005
Time Stamp:	18:35:10
Application Type:	U.S. National Stage under 35 USC 371

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File Listing:

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

Espacenet

Bibliographic data: DE 10152369 (A1)

Stable, propellant-free inhalable liquid medicament for treating asthma or chronic obstructive pulmonary disease, containing tiotropium salt and antiallergic agent, antihistamine, steroid or leukotriene antagonist

Publication date:	2002-05-08	
Inventor(s):	DRECHSEL KARIN [DE]; NIKLAUS-HUMKE BARBARA [DE]; SCHMELZER CHRISTEL [DE]; BARTH PETRA [DE] +	
Applicant(s):	BOEHRINGER INGELHEIM PHARMA [DE] +	
Classification:	- international:	***A61K31/40; A61K31/436; A61K31/4402; A61K31/4523; A61K31/46; A61K31/47; A61K31/4745; A61K31/496; A61K31/5365; A61K31/55; A61K31/56; A61K31/57; A61K31/58; A61K45/06; A61K47/10; A61K47/16; A61K47/18; A61K9/00; A61K9/08; A61K9/72; A61M15/00; A61P11/00; A61P11/06; C07D451/00;*** (IPC1-7): A61K31/5365
	- European:	A61K31/46; A61K31/496; A61K31/55; A61K31/56; A61K45/06; A61K9/00M20B5; A61K31/46; A61K31/4745; A61K31/56; A61K31/57; A61K31/58
Application number:	DE20011052369 20011024	
Priority number(s):	DE20011052369 20011024; DE20001054042 20001031	
Also published as:	• ZA 200303045 (A) • YU P33103 (A) • UY 26991 (A1) • UA 76435 (C2) • SK 5262003 (A3) • more	

Abstract of DE 10152369 (A1)

A propellant-free liquid medicament preparation (A) contains a tiotropium salt, one or more of antiallergic agents, antihistamines, steroids and/or leukotriene antagonists, water or aqueous ethanol as solvent (which dissolves (I)), acid, a preservative optionally one or more of complexants, stabilizers, co-solvents and other auxiliaries. A propellant-free liquid medicament preparation (A) contains: (1) tiotropium salt as first active agent (I), at a tiotropium concentration of 0.0005-5 wt. %; (2) one or more of antiallergic agents, antihistamines, steroids and/or leukotriene antagonists as second active agent (II); (3) water or aqueous ethanol as solvent (which dissolves (I)); (4) acid to adjust the pH to 2.0-4.5; (5) a preservative, and optionally (6) one or more of complexants, stabilizers, co-solvents and other auxiliaries. An independent claim is included for the production of (A), by mixing the individual components.

Last updated: 26.04.2011 Worldwide Database 5.7.23; 93p

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DEUTSCHES PATENT- UND MARKENAMT

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Barth, Petra, 55131 Mainz, DE

Die folgenden Angaben sind den vom Anmelder eingereichten Unterlagen entnommen

(54) Inhalative Lösungsformulierung mit einem Tiotropiumsalz

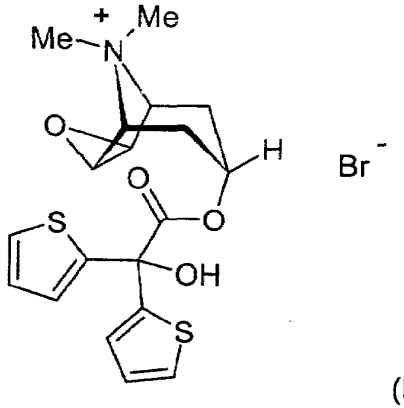
(57) Die vorliegende Erfindung betrifft eine treibgasfreie Inhalationsformulierung von in Wasser oder in einem Gemisch aus Wasser und Ethanol gelöstem Tiotropiumbromid bzw. Tiotropiumbromid-Monohydrat und daraus resultierenden treibgasfreien inhalierbaren Aerosolen.

DE 101 52 369 A 1

Beschreibung

[0001] Die vorliegende Erfindung betrifft eine treibgasfreie Inhalationsformulierung von einem in Wasser oder in einem Gemisch aus Wasser und Ethanol gelöstem pharmazeutisch akzeptablen Salz von Tiotropium in Kombination mit wenigstens einem weiteren bevorzugt inhalativ applizierbaren Wirkstoff und daraus resultierenden treibgasfreien inhalierbaren Aerosolen. Die erfindungsgemäße Formulierung eignet sich besonders zur inhalativen Applikation des Wirkstoffs, insbesondere in den Indikationen Asthma und COPD.

[0002] Tiotropium, chemisch (1α,2β,4β,5α,7β)-)-7-[(hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.0]nonane, ist als Tiotropiumbromid aus der Europäischen Patentanmeldung EP 418 716 A1 bekannt. Das Bromid-Salz des Tiotropiums weist die folgende chemische Struktur auf:



(I)

[0003] Die Verbindung besitzt wertvolle pharmakologische Eigenschaften und ist unter dem Namen Tiotropiumbromid bekannt. Tiotropium und seine Salze stellen ein hochwirksame Anticholinergika dar und können deshalb bei der Therapie von Asthma oder COPD (chronic obstructive pulmonary disease = chronisch obstruktive Lungenerkrankung) einen therapeutischen Nutzen entfalten. Pharmakologisch ebenfalls interessant ist das Monohydrat des Tiotropiumbromids.

[0004] Beide Verbindungen sind bevorzugter Gegenstand der vorliegenden Erfindung.

[0005] Die vorliegende Erfindung beschäftigt sich mit inhalativ applizierbaren flüssigen Wirkstoffformulierungen dieser Verbindungen, wobei die erfindungsgemäßen flüssigen Formulierungen hohen Qualitätsstandards genügen müssen.

[0006] Um eine optimale Wirkstoffverteilung der Wirksubstanzen in der Lunge zu erhalten, bietet sich die Applikation einer flüssigen, auf Treibgase verzichtenden, Formulierung mittels dafür geeignet Inhalatoren an. Besonders geeignet sind solche Inhalatoren, die eine kleine Menge einer flüssigen Formulierung in der therapeutisch notwendigen Dosierung binnen weniger Sekunden in ein therapeutisch-inhalativ geeignetes Aerosol vernebeln können. Im Rahmen der vorliegenden Erfindung sind solche Vernebler bevorzugt, bei denen bereits eine Menge von weniger als 100 Mikroliter, bevorzugt weniger als 50 Mikroliter, ganz bevorzugt weniger als 20 Mikroliter Wirkstofflösung mit bevorzugt einem Hub zu einem Aerosol mit einer durchschnittlichen Teilchengröße von weniger als 20 Mikrometern, bevorzugt weniger als 10 Mikrometern, so vernebelt werden können, daß der inhalierbare Anteil des Aerosols bereits der therapeutisch wirksamen Menge entspricht. Eine derartige Vorrichtung zur treibgasfreien Verabreichung einer dosierten Menge eines flüssigen Arzneimittels zur inhalativen Anwendung, wird beispielsweise in der internationalen Patentanmeldung WO 91/14468 "Atomizing Device and Methods" als auch in der WO 97/12687, dort **Fig.** 6a und 6b und der dazugehörigen. Beschreibung, ausführlich beschrieben. In einem solchen Vernebler wird eine Arzneimittellösung mittels hohen Drucks von bis zu 500 bar in ein lungengängiges Aerosol überführt und versprüht. Auf die genannten Referenzen wird im Rahmen der vorliegenden Erfindungsbeschreibung ausdrücklich in Gänze Bezug genommen.

[0007] In solchen Inhalatoren werden die Lösungsformulierungen in einem Reservoir gelagert. Dabei ist es notwendig, daß die verwendeten Wirkstoffformulierungen eine ausreichende Lagerstabilität aufweisen und gleichzeitig so beschaffen sind, daß sie dem medizinischen Zweck entsprechend möglichst ohne weitere Manipulation, direkt appliziert werden können. Ferner dürfen sie keine Bestandteile aufweisen, die so mit dem Inhalator wechselwirken können, daß der Inhalator oder die pharmazeutische Qualität der Lösung, respektive des erzeugten Aerosols, Schaden nehmen könnte.

[0008] Zur Vernebelung der Lösung wird eine spezielle Düse verwendet, wie sie beispielsweise die WO 94/07607 oder die WO 99/16530 beschreibt. Auf beide wird hiermit ausdrücklich Bezug genommen.

[0009] Die WO 98/27959 offenbart Lösungsformulierungen für den oben beschriebenen Inhalator, die als Zusatz das Dinatriumsalz der Editinsäure (Natriumedetat) enthalten. Die Schrift favorisiert für wässrige Lösungsformulierungen, die mit Hilfe des eingangs beschriebenen Inhalators in inhalierbare Aerosole versprüht werden sollen, eine Mindestkonzentration an Natriumedetat von 50 mg/100 ml um die Inzidenz von Sprühanomalien zu verringern. Unter den offenbarten Beispielen findet sich eine Formulierung mit Tiotropiumbromid. Bei dieser Formulierung ist der Wirkstoff in Wasser gelöst. Der Anteil an Natriumedetat beträgt ebenfalls 50 mg/100 ml.

[0010] Überraschend wurde jetzt gefunden, daß Lösungsformulierungen von Tiotropium-Salzen in Wasser oder einem Wasser-Ethanol-Gemisch, bei denen der Anteil des Zusatzstoffs Natriumedetat deutlich unterhalb von 50 mg/100 ml liegt, gegenüber der aus dem Stand der Technik bekannten Formulierung mit Tiotropiumbromid eine Reduktion der Streuung der ausgebrachten Masse aufweist. Zusätzlich ist die Sprayqualität sehr gut.

[0011] Das daraus resultierende Aerosol weist für die inhalative Applikation sehr gute Eigenschaften auf.

[0012] Ein weiterer Vorteil der Formulierung besteht darin, daß durch den Verzicht bzw. die Reduktion des Zusatz-

stoffs Natriumedetat in der Wirkstoffformulierung der pH-Wert der Lösungsformulierung gesenkt werden kann. Niedrige pH-Werte sind der Langzeitstabilität der Tiotropiumsalze in der Formulierung förderlich.

[0013] Es ist daher eine Aufgabe der vorliegenden Erfindung, eine wässrige Wirkstoffformulierung mit einem pharmazeutisch akzeptablen Tiotropium-Salz zu schaffen, welche den hohen Standards genügt, die notwendig sind, um eine Lösung mittels der eingangs genannten Inhalatoren optimal vernebeln zu können. Die erfindungsgemäßen Wirkstoffformulierungen müssen dabei auch eine ausreichende pharmazeutische Qualität aufweisen, d. h. sie sollten über eine Lagerzeit von einigen Jahren, bevorzugt von mindestens einem Jahr, stärker bevorzugt von zwei Jahren pharmazeutisch stabil sein.

[0014] Eine weitere Aufgabe besteht darin, treibgasfreie Lösungsformulierungen mit Tiotropiumsalzen zu schaffen, die mittels eines Inhalators unter Druck vernebelt werden, wobei die im generierten Aerosol ausgebrachte Masse reproduzierbar innerhalb eines definierten Bereichs liegt.

[0015] Eine weitere Aufgabe besteht darin, Lösungsformulierungen mit Tiotropium und einem weiteren inhalativ applizierbaren Wirkstoff zu schaffen.

[0016] Erfindungsgemäß können für die Formulierung alle pharmazeutisch akzeptablen Salze des Tiotropiums eingesetzten werden. Wird im Rahmen der vorliegenden Erfindung der Begriff Tiotropium-Salz verwendet, so ist dies als Bezugnahme auf Tiotropium zu verstehen. Eine Bezugnahme auf Tiotropium, welches das freie Ammoniumkation darstellt, entspricht erfindungsgemäß einer Bezugnahme auf Tiotropium in Form eines Salzes (Tiotropium-Salz), welches ein Anion als Gegenion enthält. Als im Rahmen der vorliegenden Erfindung einsetzbare Tiotropium-Salze sind bevorzugt Verbindungen zu verstehen, die neben Tiotropium als Gegenion (Anion) Chlorid, Bromid, Iodid, Methansulfonat, para-Toluolsulfonat und/oder Methylsulfat enthalten.

[0017] Im Rahmen der vorliegenden Erfindung ist als Salz das Tiotropiumbromid bevorzugt. Bezugnahmen auf Tiotropiumbromid sind im Rahmen der vorliegenden Erfindung stets als Bezugnahmen auf alle möglichen amorphen und kristallinen Modifikationen des Tiotropiumbromids zu verstehen. Diese können beispielsweise in der kristallinen Struktur Lösemittelmoleküle mit einschließen. Von allen kristallinen Modifikationen des Tiotropiumbromids sind erfindungsgemäß diejenigen, die Wasser mit einschließen (Hydrate) bevorzugt. Besonders bevorzugt ist im Rahmen der vorliegenden Erfindung das Tiotropiumbromid-Monohydrat einsetzbar.

[0018] In den erfindungsgemäßen Formulierungen sind Kombinationen mit einem Tiotropium-Salz und nur einem weiteren Wirkstoff bevorzugt.

[0019] In den erfindungsgemäßen Formulierungen liegen die Tiotropium-Salze in einem Lösungsmittel gelöst vor. Dabei kann das Lösungsmittel ausschließlich Wasser sein, oder es ist ein Gemisch aus Wasser und Ethanol. Ethanol kann der Formulierung zugesetzt werden, um die Löslichkeit von Zusatzstoffen oder anderen Wirkstoffen neben dem Tiotropium-Salz, bevorzugt Tiotropiumbromid, bzw. Tiotropiumbromid-Monohydrat zu erhöhen. Der relative Anteil an Ethanol gegenüber Wasser ist nicht begrenzt, er beträgt beispielsweise 90 Vol.%. Bevorzugt liegt die maximale Grenze von Ethanol bei 70 Volumenprozent, insbesondere bei 60 Volumenprozent und besonders bevorzugt bei 30 Volumenprozent. Die restlichen Volumenprozente werden von Wasser aufgefüllt. Bevorzugtes Lösungsmittel ist Wasser ohne ethanolischen Zusatz.

[0020] Die Konzentration des Tiotropium-Salzes bezogen auf den Anteil an Tiotropium in der fertigen Arzneimittelzubereitung ist abhängig von dem angestrebten therapeutischen Effekt. Für die Mehrzahl der auf Tiotropium ansprechenden Erkrankungen liegt die Konzentration an Tiotropium zwischen 0,0005 und 5 Gew.-%, bevorzugt zwischen 0,001 und 3 Gew.-%.

[0021] Der pH-Wert der erfindungsgemäßen Formulierung liegt zwischen 2,0 und 4,5, bevorzugt zwischen 2,5 und 3,5 und stärker bevorzugt zwischen 2,7 und 3,5 und besonders bevorzugt zwischen 2,7 und 3,2. Am stärksten bevorzugt sind pH-Werte mit einer oberen Grenze von 3,1.

[0022] Der pH-Wert wird durch Zugabe von pharmakologisch verträglichen Säuren eingestellt.

[0023] Beispiele für diesbezüglich bevorzugte anorganische Säuren sind: Salzsäure, Bromwasserstoffsäure, Salpetersäure, Schwefelsäure und/oder Phosphorsäure. Beispiele für besonders geeignete organische Säuren sind: Ascorbinsäure, Zitronensäure, Äpfelsäure, Weinsäure, Maleinsäure, Bernsteinsäure, Fumarsäure, Essigsäure, Ameisensäure und/oder Propionsäure und andere. Bevorzugte anorganische Säuren sind Salzsäure, Schwefelsäure. Es können auch die Säuren verwendet werden, die bereits mit dem Wirkstoff oder im Fall von Kombinationspräparaten mit einem der Wirkstoffe ein Säureadditionssalz bilden.

[0024] Unter den organischen Säuren sind Ascorbinsäure, Fumarsäure und Zitronensäure bevorzugt, insbesondere Zitronensäure. Gegebenenfalls können auch Gemische der genannten Säuren eingesetzt werden, insbesondere in Fällen von Säuren, die neben ihren Säuerungseigenschaften auch andere Eigenschaften, z. B. als Geschmacksstoffe oder Antioxidantien besitzen, wie beispielsweise Zitronensäure oder Ascorbinsäure.

[0025] Als anorganische Säuren wird ausdrücklich Salzsäure genannt.

[0026] Gegebenenfalls können auch pharmakologisch verträgliche Basen zum genauen Austitrieren des pH-Wertes eingesetzt werden. Als Basen eignen sich beispielsweise Alkalihydroxide und Alkalicarbonate. Bevorzugtes Alkaliion ist Natrium. Werden solche Basen verwendet, ist darauf zu achten, daß auch die daraus resultierenden Salze, die dann in der fertigen Arzneimittelformulierung enthalten sind, mit der oben genannten Säure pharmakologisch akzeptabel ist.

[0027] Erfindungsgemäß kann in der vorliegenden Formulierung auf den Zusatz von Editinsäure (EDTA) oder einem der bekannten Salze davon, Natriumedetat, als Stabilisator oder Komplexbildner verzichtet werden.

[0028] Eine andere bevorzugte Ausführungsform beinhaltet Editinsäure und/oder seine Salze.

[0029] In einer bevorzugten Ausführungsform mit Natriumedetat liegt der Gehalt bezogen auf Natriumedetat unter 10 mg/100 ml. In diesem Fall findet sich ein bevorzugter Bereich zwischen 5 mg/100 ml und kleiner 10 mg/100 ml oder ein anderer zwischen größer 0 und 5 mg/100 ml.

[0030] In einer anderen Ausführungsform beträgt der Gehalt an Natriumedetat 10 bis zu 30 mg/100 ml, bevorzugt beträgt er maximal 25 mg/100 ml.

[0031] In einer bevorzugten Ausführungsform wird auf diesen Zusatz gänzlich verzichtet.

[0032] Analoges wie bereits für Natriumedetat ausgeführt, gilt auch für andere vergleichbare Zusatzstoffe, die kom-

plexbildende Eigenschaften aufweisen und anstelle dessen verwendet werden können, wie beispielsweise Nitrilotriessigsäure und deren Salze.

[0033] Unter Komplexbildner werden im Rahmen der vorliegenden Erfindung bevorzugt Moleküle verstanden, die in der Lage sind Komplexbindungen einzugehen.

[0034] Bevorzugt sollen durch diese Verbindungen Kationen, besonders bevorzugt metallische Kationen komplexiert werden.

[0035] Die für ein Kombinationspräparat neben dem Tiotropium-Salz weiteren Wirkstoffe werden insbesondere aus der Klasse der Antihistaminika, Antiallergika, Leukotrien-Antagonisten und/oder Steroide ausgewählt.

[0036] Zu diesen Wirkstoffen zählen:

[0037] Als Steroide:
Alclometason,
Alclometason-dipropionat,
Alisactid,
Amcinonid,
Aminoglutethimid,
Aristocort-diacetat,
Beclometason,
Beclometason, Douglas,
Beclometason-17,21-Dipropionat,
Betamethason valerat,
Betamethasonadamantoat,
Budesonid,
Butixocort,
Canesten-HC,
Ciclometason,
Clobetasol,
Clobetason,
Cloprednol,
Cloprednol,
Cortivazol,
Deflazacort,
Deflazacort,
Demetex,
Deprodon,
Deprodon Propionat,
Dexamethason,
Dexamethason-21-isonicotinat,
Dexamethasonisonicotinat,
Diflorason,
Difluprednat,
Endrisone,
Fluazacort,
Fluclorolon acetonid,
Flunisolid,
Fluocinolon acetonid,
Fluocortin butyl,
Fluocinonid,
Fluocortin,
Fluocortoloncapronat,
Fluodexan,
Fluorometholon,
Fluticason,
Fluticason-propionat,
Formebolon,
Formocortal,
Halcinonid,
Halometason,
Halopredon-acetat,
Hydrocortison,
Hydrocortison-17-Butyrat,
Hydrocortison-aceponat,
Hydrocortison-butyratpropionat,
Icomethason enbutat,
Ciclometason,
Lotrison,
Mazipredon,
Medryson,
Meprednison,

Methylprednisolon-Aceponat,
Mometason,
Mometason furoat,
Mycophenolate mofetil
Pranlukast,
Paramethason-acetat,
Prednicarbat,
Promedrol,
Seratrodast,
Tipredan,
Tixocortol-pivalat,
Triamcinolon,
Triamcinolon-Hexacetonid,
Trilostan,
Trimacinolon Benetonid,
Ulobetasol-propionat,
Zileuton

[0038] 9-alpha-chloro-6-alpha-fluoro-11-beta-17-alpha-dihydroxy-16-alpha-methyl-3-oxo-1,4-androstadien-17-beta-carboxysäure-methylester-17-propionat.

[0039] Besonders bevorzugt sind die Kombination Tiotropiumbromid, bzw. Tiotropiumbromid-Monohydrat und Budesonid, Flunisolid, Beclometasondipropionat oder Fluticason, sowie pharmakologisch verträgliche (ggf. andere) Salze davon.

[0040] Bei der bevorzugten Kombination handelt es sich um Tiotropiumbromid, bzw. Tiotropiumbromid-Monohydrat und Budesonid.

[0041] Die Konzentration des Steroids, beispielsweise Budesonid, Flunisolid, Beclometasondipropionat oder Fluticason, in den erfindungsgemäßen Formulierungen beträgt bevorzugt 0,05 bis 10 Gew.-%, bevorzugt bis 5 Gew.-%, stärker bevorzugt 0,1 bis 2,5 Gew.-%, besonders bevorzugt 0,2 bis 2,5 Gew.-%. Bei Verwendung der Formulierung mit dem eingangs genannten Inhalator wird die Konzentration an Steroid bevorzugt so eingestellt, daß pro Hub 12,5 bis 250 Mikrogramm Steroid vernebelt werden. Besonders bevorzugt sind Konzentrationen, bei denen die pharmakologisch aktive Dosis innerhalb von ein oder zwei Hüben verabreicht wird.

[0042] Enthält die Kombinationsformulierung einen Leukotrienantagonisten, so ist dieser bevorzugt ausgewählt aus der Gruppe Montelukast, Pranlukast, Zafirlukast, 1-(((R)-(3-(2-(6,7-Difluoro-2-chinolinyl)ethenyl)phenyl)-3-(2-(2-hydroxy-2-propyl)phenyl)thio)methylcyclopropanessigsäure, 1-(((R)-3-(3-(2-(2,3-dichlorothieno[3,2-b]pyridin-5-yl)-(E)-ethenyl)phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl)propyl)thio)methyl)cycloprpanessigsäure, [2-[[2-(4-tert-butyl-2-thiazolyl)-5-benzofuranyl]oxymethyl]phenyl]essigsäure. Bevorzugt sind Montelukast, Pranlukast und/oder Zafirlukast.

[0043] Die Konzentration des Leukotrienantagonisten beträgt dabei 0,05 bis 10 Gew.-%, bevorzugt bis 5 Gew.-%, stärker bevorzugt 0,1 bis 3,5 Gew.-%.

[0044] Als Antihistaminika und Antiallergika seien genannt:
Azelastin,
Astemizol,
Bamipin,
Carbinoxaminhydrogen-maleat,
Cetirizin,
Cexchlorpheniramin,
Chlorphenoxamin,
Clemastin,
Clemastinhydrogen-fumarat,
Desloratidin,
Dimenhydrinat,
Dimetinden,
Dinatriumcromoglikat,
Diphenhydramin,
Doxylamin,
Ebastin,
Emedastin,
Epinastin,
Fexofenadin,
Ketotifen,
Levocabastin,
Loratadin,
Meclozin,
Meqitazin,
Mizolastin,
Nedocromil,
Pheniramin und/oder
Promethazin

[0045] Bevorzugt sind Epinastin, Nedocromil, Dinatrumcromoglicat, Astemizol, Mequitazin, Carbinoxamin und/oder

Clemastin und/oder die entsprechenden pharmazeutisch akzeptablen Salze.

[0046] Im Kombinationspräparat beträgt die Konzentration der Antiallergika und/oder Antihistaminika bevorzugt 0,05 bis 15 Gew.-%, bevorzugt bis 10 Gew.-%, stärker bevorzugt 0,1 bis 10 Gew.-%, besonders bevorzugt 0,1 bis 7 Gew.-%.

[0047] Alle genannten Wirkstoffe können ggf. auch in Form ihrer pharmakologisch verträglichen Salze eingesetzt werden.

[0048] Bei den Kombinationspräparaten handelt es sich bevorzugt um Formulierungen, bei denen Tiotropium gelöst vorliegt. Der andere Wirkstoff kann gelöst oder suspendiert sein, was in der Regel von dem weiteren Wirkstoff und vom Lösungsmittel bestimmt wird.

[0049] Ist der weitere Wirkstoff eine bei geringen pH-Werten empfindliche Substanz, so wird dieser bevorzugt als Suspension formuliert. Der Vorteil eines Suspensats besteht darin, daß der pH-Wert stärker sauer eingestellt werden kann, was der Stabilität des gelösten Tiotropiums dienlich ist. Der bevorzugte pH-Bereich von Tiotropiumbromid liegt zwischen 2,0 und 4,5, bevorzugt 2,5 und 3,5, besonders bevorzugt zwischen 2,7 und 3,2.

[0050] Im Fall der Steroide liegen diese bevorzugt als Suspensat vor, insbesondere Fluticason. Dies gilt insbesondere, wenn als Lösungsmittel nur Wasser ohne Ethanol verwendet wird. Bei Zusatz von Ethanol, kann das Steroid auch als Lösung formuliert werden.

[0051] Es hat sich aber gezeigt, daß z. B. Budesonid auch bei pH-Werten von 3,5 ausreichend stabil ist, wenn es in einem Gemisch aus Wasser und Ethanol gelöst vorliegt.

[0052] Im Hinblick auf die Verwendung der erfindungsgemäßen Formulierungen in dem im Rahmen der vorliegenden Erfindung beschriebenen Inhalator kann es vorteilhaft sein, wenn alle Bestandteile der Formulierung gelöst vorliegen.

[0053] Der erfindungsgemäßen Formulierung können neben Ethanol weitere Co-Solventien und/oder weitere Hilfsstoffe zugesetzt werden.

[0054] Bevorzugte weitere Co-Solventien sind solche, die Hydroxylgruppen oder andere polare Gruppen enthalten, beispielsweise Alkohole – insbesondere Isopropylalkohol, Glykole – insbesondere Propylenglykol, Polyethylenglykol, Polypropylenglykol, Glykolether, Glycerol, Polyoxyethylenalkohole und Polyoxyethylen-Fettsäureester.

[0055] Unter Hilfs- und Zusatzstoffen wird in diesem Zusammenhang jeder pharmakologisch verträgliche und therapeutisch sinnvolle Stoff verstanden, der kein Wirkstoff ist, aber zusammen mit dem (den) Wirkstoff(en) in dem pharmakologisch geeigneten Lösungsmittel formuliert werden kann, um die qualitativen Eigenschaften der Wirkstoffformulierung zu verbessern. Bevorzugt entfalten diese Stoffe keine oder im Kontext mit der angestrebten Therapie keine nennenswerte oder zumindest keine unerwünschte pharmakologische Wirkung. Zu den Hilfs- und Zusatzstoffen zählen z. B. oberflächenaktive Stoffe, wie z. B. Sojalecithin, Ölsäure, Sorbitanester, wie Sorbitantrioleat, Polyvinylpyrrolidon sonstige Stabilisatoren, Komplexbildner, Antioxidantien und/oder Konservierungsstoffe, die die Verwendungsdauer der fertigen Arzneimittelformulierung verlängern, Geschmacksstoffe, Vitamine und/oder sonstige dem Stand der Technik bekannte Zusatzstoffe. Zu den Zusatzstoffen zählen auch pharmakologisch unbedenkliche Salze wie beispielsweise Natriumchlorid.

[0056] Als oberflächenaktive Mittel oder Suspensions-stabilisierenden Agentien eignen sich alle pharmakologisch verträglichen Stoffe, die einen lipophilen Kohlenwasserstoffrest und eine oder mehrere funktionelle hydrophile Gruppe(n) verfügen, insbesondere geeignet sind C_{5-20}-Fettalkohole, C_{5-20}-Fettsäuren, C_{5-20}-Fettsäureester, Lecithin, Glyceride, Propyleneglycolester, Polyoxyethylene, Polysorbate, Sorbitanester und/oder Kohlenhydrate. Bevorzugt sind C_{5-20}-Fettsäuren, Propylenglyoldiester und/oder Triglyceride und/oder Sorbitane der C_{5-20}-Fettsäuren, besonders bevorzugt sind Ölsäure und Sorbitan-mono-, -di- oder -trioleate. Alternativ können auch toxikologisch und pharmazeutisch unbedenkliche Polymere und/oder Blockpolymere als Suspensions-stabilisierenden Agentien verwendet werden.

[0057] Die Menge an oberflächenaktiven Mittel kann bis zu 1 : 1 bezogen auf den Gewichtsanteil der suspendierten Wirkstoffe betragen, bevorzugt sind Mengen von 0,0001 : 1 bis zu 0,5 : 1 und besonders bevorzugt Mengen von 0,0001 : 1 bis zu 0,25 : 1.

[0058] Zu den bevorzugten Hilfsstoffen zählen Antioxidantien, wie beispielsweise Ascorbinsäure, sofern nicht bereits für die Einstellung des pH-Werts verwendet, Vitamin A, Vitamin E, Tocopherole und ähnliche im menschlichen Organismus vorkommende Vitamine oder Provitamine.

[0059] Konservierungsstoffe können eingesetzt werden, um die Formulierung vor Kontamination mit pathogenen Keimen zu schützen. Als Konservierungsstoffe eignen sich die dem Stand der Technik bekannten, insbesondere Benzalkoniumchlorid oder Benzoesäure bzw. Benzoate wie Natriumbenzoat in der aus dem Stand der Technik bekannten Konzentration.

[0060] Bevorzugte Formulierungen enthalten außer dem Lösungsmittel Wasser und/oder Wasser/Ethanol und dem Tiotropiumsalz nur noch Benzalkoniumchlorid, eine Säure zum Einstellen des pH-Werts und Natriumedetat.

[0061] In einer anderen bevorzugten Ausführungsform wird auf Natriumedetat verzichtet. Gegebenenfalls können diese Ausführungsformen auch Natriumchlorid enthalten.

[0062] Wie bereits mehrfach erwähnt, wird Tiotropiumbromid in der EP 418 716 A1, beschrieben, kristallines Tiotropiumbromid-Monohydrat kann mittels eines Herstellverfahrens, welches nachfolgend detaillierter beschrieben wird, erhalten werden.

[0063] Zur Herstellung des kristallinen Monohydrats gemäß der vorliegenden Erfindung ist es erforderlich, Tiotropiumbromid, welches beispielsweise nach der in der EP 418 716 A1 offenbarten Herstellungsvorschrift erhalten worden ist, in Wasser aufzunehmen, zu Erwärmen, eine Reinigung mit Aktivkohle durchzuführen und nach Abtrennen der Aktivkohle unter langsamem Abkühlen das Tiotropiumbromid-Monohydrat langsam zu kristallisieren.

[0064] Bevorzugt wird wie nachfolgend beschrieben vorgegangen.

[0065] In einem geeignet dimensionierten Reaktionsgefäß wird das Lösemittel mit Tiotropiumbromid, welches beispielsweise nach der in der EP 418 716 A1 offenbarten Herstellungsvorschrift erhalten worden ist, gemischt.

[0066] Pro Mol eingesetztes Tiotropiumbromid werden 0,4 bis 1,5 kg, bevorzugt 0,6 bis 1 kg, besonders bevorzugt ca. 0,8 kg Wasser als Lösemittel verwendet.

[0067] Die erhaltene Mischung wird unter Rühren erwärmt, vorzugsweise auf mehr als 50°C, besonders bevorzugt auf

mehr als 60°C. Die maximal wählbare Temperatur bestimmt sich durch den Siedepunkt des verwendeten Lösemittels Wasser.

[0068] Vorzugsweise wird die Mischung auf einen Bereich von 80–90°C erhitzt.

[0069] In diese Lösung wird Aktivkohle, trocken oder wasserfeucht, eingebracht. Bevorzugt werden pro Mol eingesetztes Tiotropiumbromid 10 bis 50 g, besonders bevorzugt 15 bis 35 g, höchst bevorzugt etwa 25 g Aktivkohle eingesetzt. Gegebenenfalls wird die Aktivkohle vor Einbringen in die Tiotropiumbromid-haltige Lösung in Wasser aufgeschlämmt. Pro Mol eingesetztes Tiotropiumbromid werden zum Aufschlämmen der Aktivkohle 70 bis 200 g, bevorzugt 100 bis 160 g, besonders bevorzugt ca. 135 g Wasser verwendet. Wird die Aktivkohle vor Einbringen in die Tiotropiumbromidhaltige Lösung zuvor in Wasser aufgeschlämmt, empfiehlt es sich, mit der gleichen Menge Wasser nachzuspülen.

[0070] Bei konstanter Temperatur wird nach erfolgter Aktivkohlezugabe zwischen 5 bis 60 Minuten, bevorzugt zwischen 10 und 30 Minuten, besonders bevorzugt etwa 15 Minuten weitergerührt und die erhaltene Mischung filtriert, um die Aktivkohle zu entfernen. Der Filter wird anschließend mit Wasser nachgespült. Hierfür werden pro Mol eingesetztes Tiotropiumbromid 140 bis 400 g, bevorzugt 200 bis 320 g, höchst bevorzugt ca. 270 g Wasser verwendet.

[0071] Das Filtrat wird anschließend langsam abgekühlt, vorzugsweise auf eine Temperatur von 20–25°C. Die Abkühlung wird vorzugsweise mit einer Abkühlrate von 1 bis 10°C pro 10 bis 30 Minuten, bevorzugt von 2 bis 8°C pro 10 bis 30 Minuten, besonders bevorzugt von 3 bis 5°C pro 10 bis 20 Minuten, höchst bevorzugt von 3 bis 5°C pro ca. 20 Minuten durchgeführt. Gegebenenfalls kann sich nach dem Abkühlen auf 20 bis 25°C eine weitere Abkühlung auf unter 20°C, besonders bevorzugt auf 10 bis 15°C anschließen.

[0072] Nach erfolgter Abkühlung wird zwischen 20 Minuten und 3 Stunden, vorzugsweise zwischen 40 Minuten und 2 Stunden, besonders bevorzugt etwa eine Stunde zur Vervollständigung der Kristallisation nachgerührt.

[0073] Die entstandenen Kristalle werden abschließend durch Filtrieren oder Absaugen des Lösemittels isoliert. Sollte es erforderlich sein, die erhaltenen Kristalle einem weiteren Waschschritt zu unterwerfen, empfiehlt es sich als Waschlösemittel Wasser oder Aceton zu verwenden. Pro Mol eingesetztes Tiotropiumbromid können zum Waschen der erhaltenen Tiotropiumbromid-monohydrat-Kristalle 0,1 bis 1,0 L, bevorzugt 0,2 bis 0,5 L, besonders bevorzugt etwa 0,3 L Lösemittel Verwendung finden. Gegebenenfalls kann der Waschschritt wiederholt durchgeführt werden. Das erhaltene Produkt wird im Vakuum oder mittels erwärmter Umluft bis zum Erreichen eines Wassergehalts von 2,5–4,0% getrocknet.

[0074] Ein Aspekt der vorliegenden Erfindung betrifft daher auch Lösungsformulierungen der oben beschriebenen Art, bei denen kristallines Tiotropiumbromid-Monohydrat eingesetzt wird, welches gemäß vorstehend beschriebener Vorgehensweise erhältlich ist.

[0075] Die erfindungsgemäßen Arzneimittelformulierungen mit Tiotropium-Salzen werden bevorzugt in einem Inhalator der vorstehend beschriebenen Art verwendet, um daraus die erfindungsgemäßen treibgasfreien Aerosole herzustellen. An dieser Stelle sei deshalb noch einmal ausdrücklich auf die eingangs beschriebenen Patentdokumente verwiesen, auf die hiermit Bezug genommen wird.

[0076] Wie eingangs geschildert wird eine weiterentwickelte Ausführungsform des bevorzugten Inhalators in der WO 97/12687 und deren **Fig.** 6 offenbart. Dieser Vernebler (Respimat®) kann vorteilhaft zur Erzeugung der erfindungsgemäßen inhalierbaren Aerosole mit einem Tiotropium-Salz als Wirkstoff eingesetzt werden. Aufgrund seiner zylinderähnlichen Form und einer handlichen Größe von weniger als 9 bis 15 cm in der Länge und 2 bis 4 cm in der Breite kann dieses Device jederzeit vom Patienten mitgeführt werden. Der Vernebler versprüht ein definiertes Volumen der Arzneimittelformulierung unter Anwendung hoher Drücke durch kleine Düsen, so daß inhalierbare Aerosole entstehen.

[0077] Im wesentlichen besteht der bevorzugte Zerstäuber aus einem Gehäuseoberteil, einem Pumpengehäuse, einer Düse, einem Sperrspannwerk, einem Federgehäuse, einer Feder und einem Vorratsbehälter, gekennzeichnet durch

- ein Pumpengehäuse, das im Gehäuseoberteil befestigt ist, und das an seinem einen Ende einen Düsenkörper mit der Düse bzw. Düsenanordnung trägt,
- einen Hohlkolben mit Ventilkörper,
- einen Abtriebsflansch, in dem der Hohlkolben befestigt ist, und der sich im Gehäuseoberteil befindet,
- ein Sperrspannwerk, das sich im Gehäuseoberteil befindet,
- ein Federgehäuse mit der darin befindlichen Feder, das am Gehäuseoberteil mittels eines Drehlagers drehbar gelagert ist,
- ein Gehäuseunterteil, das auf das Federgehäuse in axialer Richtung aufgesteckt ist.

[0078] Der Hohlkolben mit Ventilkörper entspricht einer in der WO 97/12687 offenbarten Vorrichtungen. Er ragt teilweise in den Zylinder des Pumpengehäuses hinein und ist im Zylinder axial verschiebbar angeordnet. Insbesondere wird auf die **Fig.** 1–4 – insbesondere **Fig.** 3 – und die dazugehörigen Beschreibungsteile Bezug genommen. Der Hohlkolben mit Ventilkörper übt auf seiner Hochdruckseite zum Zeitpunkt des Auslösens der Feder einen Druck von 5 bis 60 Mpa (etwa 50 bis 600 bar), bevorzugt 10 bis 60 Mpa (etwa 100 bis 600 bar) auf das Fluid, die abgemessene Wirkstofflösung aus. Dabei werden Volumina von 10 bis 50 Mikroliter bevorzugt, besonders bevorzugt sind Volumina von 10 bis 20 Mikroliter, ganz besonders bevorzugt ist ein Volumen von 15 Mikroliter pro Hub.

[0079] Der Ventilkörper ist bevorzugt an dem Ende des Hohlkolbens angebracht, das dem Düsenkörper zugewandt ist.

[0080] Die Düse im Düsenkörper ist bevorzugt mikrostrukturiert, d. h. durch Mikrotechnik hergestellt. Mikrostrukturierte Düsenkörper sind beispielsweise in der WO-94/07607, sowie in der WO 99/16530 offenbart; auf die hiermit inhaltlich Bezug genommen wird, insbesondere auf **Fig.** 1 der WO-94/07607 und deren Beschreibung.

[0081] Der Düsenkörper besteht z. B. aus zwei fest miteinander verbundenen Platten aus Glas und/oder Silizium, von denen wenigstens eine Platte einen oder mehrere mikrostrukturierte Kanäle aufweist, die die Düseneinlaßseite mit der Düsenauslaßseite verbinden. Auf der Düsenauslaßseite ist mindestens eine runde oder nicht-runde Öffnung von 2 bis 10 Mikrometer Tiefe und 5 bis 15 Mikrometern Breite, wobei die Tiefe bevorzugt bei 4, 5 bis 6,5 Mikrometern und die Länge bei 7 bis 9 Mikrometern beträgt.

[0082] Im Fall von mehreren Düsenöffnungen, bevorzugt sind zwei, können die Strahlrichtungen der Düsen im Düsen-

körper parallel zueinander verlaufen oder sie sind in Richtung Düsenöffnung gegeneinander geneigt. Bei einem Düsenkörper mit mindestens zwei Düsenöffnungen auf der Auslaßseite können die Strahlrichtungen mit einem Winkel von 20 Grad bis 160 Grad gegeneinander geneigt sein, bevorzugt wird ein Winkel von 60 bis 150 Grad, insbesondere bevorzugt 80 bis 100°.

[0083] Die Düsenöffnungen sind bevorzugt in einer Entfernung von 10 bis 200 Mikrometern angeordnet, stärker bevorzugt in einer Entfernung von 10 bis 100 Mikrometer, besonders bevorzugt 30 bis 70 Mikrometer. Am stärksten bevorzugt sind 50 Mikrometer.

[0084] Die Strahlrichtungen treffen sich dementsprechend in der Umgebung der Düsenöffnungen.

[0085] Die flüssige Arzneimittelzubereitung trifft wie bereits erwähnt mit einem Eingangsdruck von bis zu 600 bar, bevorzugt 200 bis 300 bar auf den Düsenkörper und wird über die Düsenöffnungen in ein inhalierbares Aerosol zerstäubt. Die bevorzugten Teilchengrößen des Aerosols liegen bei bis zu 20 Mikrometern, bevorzugt 3 bis 10 Mikrometern.

[0086] Das Sperrspannwerk enthält eine Feder, bevorzugt eine zylindrische schraubenförmige Druckfeder, als Speicher für die mechanische Energie. Die Feder wirkt auf den Abtriebsflansch als Sprungstück, dessen Bewegung durch die Position eines Sperrglieds bestimmt wird. Der Weg des Abtriebsflansches wird durch einen oberen und einen unteren Anschlag präzise begrenzt. Die Feder wird bevorzugt über ein kraftübersetzendes Getriebe, z. B. ein Schraubschubgetriebe, durch ein äußeres Drehmoment gespannt, das beim Drehen des Gehäuseoberteils gegen das Federgehäuse im Gehäuseunterteil erzeugt wird. In diesem Fall enthalten das Gehäuseoberteil und der Abtriebsflansch ein ein- oder mehrgängiges Keilgetriebe.

[0087] Das Sperrglied mit einrückenden Sperrflächen ist ringförmig um den Abtriebsflansch angeordnet. Es besteht z. B. aus einem in sich radial elastisch verformbaren Ring aus Kunststoff oder aus Metall. Der Ring ist in einer Ebene senkrecht zur Zerstäuberachse angeordnet. Nach dem Spannen der Feder schieben sich die Sperrflächen des Sperrgliedes in den Weg des Abtriebsflansches und verhindern das Entspannen der Feder. Das Sperrglied wird mittels einer Taste ausgelöst. Die Auslösetaste ist mit dem Sperrglied verbunden oder gekoppelt. Zum Auslösen des Sperrspannwerkes wird die Auslösetaste parallel zur Ringebene, und zwar bevorzugt in den Zerstäuber hinein, verschoben; dabei wird der verformbare Ring in der Ringebene verformt. Konstruktive Details des Sperrspannwerkes sind in der WO 97/20590 beschrieben.

[0088] Das Gehäuseunterteil wird in axialer Richtung über das Federgehäuse geschoben und verdeckt die Lagerung, den Antrieb der Spindel und den Vorratsbehälter für das Fluid.

[0089] Beim Betätigen des Zerstäubers wird das Gehäuseoberteil gegen das Gehäuseunterteil gedreht, wobei das Gehäuseunterteil das Federgehäuse mitnimmt. Dabei wird die Feder über das Schraubschubgetriebe zusammengedrückt und gespannt, und das Sperrwerk rastet selbsttätig ein. Der Drehwinkel ist bevorzugt ein ganzzahliger Bruchteil von 360 Grad, z. B. 180. Grad. Gleichzeitig mit dem Spannen der Feder wird das Abtriebsteil im Gehäuseoberteil um einen vorgegebenen Weg verschoben, der Hohlkolben wird innerhalb des Zylinders im Pumpengehäuse zurückgezogen, wodurch eine Teilmenge des Fluids aus dem Vorratsbehälter in den Hochdruckraum vor der Düse eingesaugt wird.

[0090] In den Zerstäuber können gegebenenfalls nacheinander mehrere das zu zerstäubende Fluid enthaltende austauschbare Vorratsbehälter eingeschoben und benutzt werden. Der Vorratsbehälter enthält die erfindungsgemäße wässerige Aerosolzubereitung.

[0091] Der Zerstäubungsvorgang wird durch leichtes Eindrücken der Auslösetaste eingeleitet. Dabei gibt das Sperrwerk den Weg für das Abtriebsteil frei. Die gespannte Feder schiebt den Kolben in den Zylinder des Pumpengehäuses hinein. Das Fluid tritt aus der Düse des Zerstäubers in zerstäubter Form aus.

[0092] Weitere konstruktive Details sind in den PCT-Anmeldungen WO 97/12683 und WO 97/20590 offenbart, auf die hiermit inhaltlich Bezug genommen wird.

[0093] Die Bauteile des Zerstäubers (Verneblers) sind aus einem der Funktion entsprechend geeignetem Material. Das Gehäuse des Zerstäubers und – so weit es die Funktion erlaubt – auch andere Teile sind bevorzugt aus Kunststoff, z. B. im Spritzgießverfahren, hergestellt. Für medizinische Zwecke werden physiologisch unbedenkliche Materialien verwendet.

[0094] In den **Fig.** 1a/b, die identisch sind mit den **Fig.** 6a/b der WO 97/12687, ist der Vernebler (Respimat®) beschrieben, mit dem die erfindungsgemäßen wäßrigen Aerosolzubereitungen vorteilhaft inhaliert werden können.

[0095] **Fig.** 1a zeigt einen Längsschnitt durch den Zerstäuber bei gespannter Feder, **Fig.** 1b zeigt einen Längsschnitt durch den Zerstäuber bei entspannter Feder.

[0096] Das Gehäuseoberteil (**51**) enthält das Pumpengehäuse (**52**), an dessen Ende der Halter (**53**) für die Zerstäuberdüse angebracht ist. In dem Halter befindet sich der Düsenkörper (**54**) und ein Filter (**55**). Der im Abtriebsflansch (**56**) des Sperrspannwerkes befestigte Hohlkolben (**57**) ragt teilweise in den Zylinder des Pumpengehäuses hinein. An seinem Ende trägt der Hohlkolben den Ventilkörper (**58**). Der Hohlkolben ist mittels der Dichtung (**59**) abgedichtet. Innerhalb des Gehäuseoberteils befindet sich der Anschlag (**60**), an dem der Abtriebsflansch bei entspannter Feder anliegt. Am Abtriebsflansch befindet sich der Anschlag (**61**), an dem der Abtriebsflansch bei gespannter Feder anliegt. Nach dem Spannen der Feder schiebt sich das Sperrglied (**62**) zwischen den Anschlag (**61**) und eine Abstützung (**63**) im Gehäuseoberteil. Die Auslösetaste (**64**) steht mit dem Sperrglied in Verbindung. Das Gehäuseoberteil endet im Mundstück (**65**) und ist mit der aufsteckbaren Schutzkappe (**66**) verschlossen.

[0097] Das Federgehäuse (**67**) mit Druckfeder (**68**) ist mittels der Schnappnasen (**69**) und Drehlager am Gehäuseoberteil drehbar gelagert. Über das Federgehäuse ist das Gehäuseunterteil (**70**) geschoben. Innerhalb des Federgehäuses befindet sich der austauschbare Vorratsbehälter (**71**) für das zu zerstäubende Fluid (**72**). Der Vorratsbehälter ist mit dem Stopfen (**73**) verschlossen, durch den der Hohlkolben in den Vorratsbehälter hineinragt und mit seinem Ende in das Fluid (Vorrat an Wirkstofflösung) eintaucht.

[0098] In der Mantelfläche des Federgehäuses ist die Spindel (**74**) für das mechanische Zählwerk angebracht. An dem Ende der Spindel, das dem Gehäuseoberteil zugewandt ist, befindet das Antriebsritzel (**75**). Auf der Spindel sitzt der Reiter (**76**).

[0099] Der oben beschriebene Vernebler ist geeignet, die erfindungsgemäßen Aerosolzubereitungen zu einem für die Inhalation geeignetem Aerosol zu vernebeln.

[0100] Wird die erfindungsgemäße Formulierung mittels der vorstehend beschriebenen Technik (Respimat®) vernebelt, sollte die ausgebrachte Masse bei wenigstens 97%, bevorzugt wenigstens 98% aller Betätigungen des Inhalators (Hube) einer definierten Menge mit einem Toleranzbereichs von maximal 25%, bevorzugt 20% dieser Menge entsprechen. Bevorzugt werden pro Hub zwischen 5 und 30 mg Formulierung als definierte Masse ausgebracht, besonders bevorzugt zwischen 5 und 20 mg.

[0101] Der Anteil der ausgebrachten Masse, der außerhalb einer Toleranzgrenze von maximal 25% zur erwünschten Masse liegt, sollte unter 1,5%, bevorzugt unter 1,2% betragen.

[0102] Die erfindungsgemäße Formulierung kann jedoch auch mittels anderer als der vorstehend beschriebenen Inhalatoren, beispielsweise Jet-Stream-Inhalatoren, vernebelt werden.

Beispiele

I. Synthesebeispiel für Tiotropiumbromid-Monohydrat

[0103] In einem geeigneten Reaktionsgefäß werden in 25,7 kg Wasser 15,0 kg Tiotropiumbromid eingetragen. Die Mischung wird auf 80–90°C erhitzt und bei gleichbleibender Temperatur solange gerührt, bis eine klare Lösung entsteht. Aktivkohle (0,8 kg), wasserfeucht, wird in 4,4 kg Wasser aufgeschlämmt, diese Mischung in die Tiotropiumbromid-haltige Lösung eingetragen und mit 4,3 kg Wasser nachgespült. Die so erhaltene Mischung wird wenigstens 15 Min. bei 80–90°C gerührt und anschließend über einen beheizten Filter in einen auf 70°C Manteltemperatur vorgewärmten Apparat filtriert. Der Filter wird mit 8,6 kg Wasser nachgespült. Der Apparateinhalt wird mit 3–5°C pro 20 Minuten auf eine Temperatur von 20–25°C abgekühlt. Mit Kaltwasserkühlung wird der Apparat auf 10–15°C weiter abgekühlt und die Kristallisation durch mindestens einstündiges Nachrühren vervollständigt. Das Kristallisat wird über einen Nutschentrockner isoliert, der isolierte Kristallbrei mit 9 L kaltem Wasser (10–15°C) und kaltem Aceton (10–15°C) gewaschen. Die erhaltenen Kristalle werden bei 25°C über 2 Stunden im Stickstoffstrom getrocknet.
Ausbeute: 13,4 kg Tiotropiumbromid-Monohydrat (86% d. Th.)

II. Formulierungsbeispiele

100 g Arzneimittelzubereitung enthalten

Beispiel	Menge an Tiotropium-bromid mit einem Anteil bezogen auf Tiotropium:	Menge an Tiotropium-bromid-Monohydrat mit einem Anteil bezogen auf Tiotropium:	Menge an Benzalkonium-chlorid	Menge an Natrium-edetat	pH-Wert, eingestellt mit HCl (1N)
1	0,099 g	---	10 mg	25 mg	3,0
2	0,006 g	---	10 mg	25 mg	3,0
3	0,099 g	---	10 mg	10 mg	3,0
4	0,006 g	---	10 mg	10 mg	3,0
5	---	0,099 g	10 mg	25 mg	3,0
6	---	0,006 g	10 mg	25 mg	3,0
7	---	0,099 g	10 mg	10 mg	3,0
8	---	0,006 g	10 mg	10 mg	3,0

[0104] Der restliche Bestandteil ist Wasser oder Wasser/Ethanol und einer der oben genannten Wirkstoffe in einer aus dem Stand der Technik bekannten Menge.

Beispiele 9 bis 12: Budesonid

[0105] Jedes der Beispiele 1 bis 8 kann zusätzlich enthalten:
Beispiel 9a: Budesonid: 0,3 g, pH, eingestellt mit HCl: 3,0, Lösungsmittel nur Wasser, kein Ethanol;
Beispiel 9b: Budesonid: 0,3 g, pH, eingestellt mit HCl: 3,5;
Beispiel 9c: Budesonid: 0,3 g, pH, eingestellt mit HCl: 4,0;
Beispiel 10: analog Beispiel 9a bis 9c mit Budesonid: 0,6 g,
Beispiel 11: analog Beispiel 9a bis 9c mit Budesonid: 1,3 g,
Beispiel 12: analog Beispiel 9a bis 9c mit Budesonid: 2,0 g.

[0106] In den Beispielen 9 bis 12 liegt das Steroid in der Formulierung als Suspensat vor. Als oberflächenaktives Mittel kann Sorbitantrioleat eingesetzt werden.

Beispiele 13 bis 15

[0107] Analog Beispiele 9 bis 12. Benzalkoniumchlorid wird gegen Natriumbenzoat ausgetauscht.

Beispiele 16 bis 19

[0108] Analog Beispiele 9 bis 12. Anstelle der Salzsäure wird ausschließlich Zitronensäure zum Einstellen des pH-Werts verwendet.

Beispiele 20 bis 30

[0109] Die Bestandteile und Mengen sind analog den Beispielen 9 bis 19.

[0110] Anstelle von Wasser wird ein Gemisch aus Wasser (10 Vol.%) und Ethanol (90 Vol.%) verwendet. Budesonid liegt gelöst vor.

Weitere Beispiele

[0111] Analog den oben beschriebenen Beispielen 9 bis 30 wird anstelle von Budesonid, die gleiche Menge an Flunisolid, Beclometasondipropionat oder Fluticason eingesetzt. Im Fall von Fluticason wird im Fall des Suspensionsformulierung bevorzugt Lecithin anstelle des Sorbitantrioleats hinzugegeben. Die Steroide werden als Suspension formuliert, für den Fall, daß als Lösungsmittel nur Wasser eingesetzt wird. Im Fall eines Gemischs aus Wasser und Ethanol kann das Steroid gelöst sein.

Beispiel 31

Epinastin: 0,2 g
EDTA: 25 mg
Tiotropiumbromid-Monohydrat: 29 mg,
0,1 n Salzsäure zum Einstellen eines pH-Werts von 3,0,
Wasser ad 100 ml.

Patentansprüche

1. Flüssige, treibgasfreie Arzneimittelzubereitung aus wenigstens zwei kombinierbaren Wirkstoffen beinhaltend
ein Tiotropium-Salz als einer der Wirkstoffe, in einer Konzentration bezogen auf Tiotropium zwischen 0,0005 und 5 Gew.-%,
einen weiteren Wirkstoff aus der Gruppe der Antiallergika, Antihistaminika, Steroide und/oder Leukotrien-Antagonisten,
Wasser oder ein Wasser/Ethanol-Gemisch als Lösungsmittel, wobei zumindest das Tiotropium-Salz darin gelöst ist,
Säure zum Einstellen eines pH-Werts zwischen 2,0 und 4,5,
ein pharmakologisch verträglichen Konservierungsmittel,
optional einen pharmakologisch akzeptablen Komplexbildner und/oder Stabilisator und/oder einen pharmakologisch akzeptablen Co-Solvens und/oder andere pharmakologisch akzeptablen Hilfs- und Zusatzstoffen neben dem Konservierungsmittel.

2. Arzneimittelzubereitung nach Anspruch 1, dadurch gekennzeichnet, daß das Tiotropium-Salz ein Salz mit HBr, HCl, HJ, Monomethylschwefelsäureester, Methansulfonsäure und/oder p-Toluolsulfonsäure ist.

3. Arzneimittelzubereitung nach Anspruch 1, dadurch gekennzeichnet, daß der Wirkstoff Tiotropiumbromid ist.

4. Arzneimittelzubereitung nach Anspruch 1, dadurch gekennzeichnet, daß der Wirkstoff Tiotropiumbromid-Monohydrat ist.

5. Arzneimittelzubereitung nach einem der Ansprüche 1 bis 4, dadurch gekennzeichnet, daß das Lösungsmittel Wasser ist.

6. Arzneimittelzubereitung nach einem der Ansprüche 1 bis 4, dadurch gekennzeichnet, daß das Lösungsmittel ein Wasser-Ethanol-Gemisch ist mit bevorzugt bis zu 90 Vol.% Ethanol, besonders bevorzugt bis zu 70 Vol.% Ethanol und ganz besonders bevorzugt bis zu 30 Vol.% Ethanol.

7. Arzneimittelzubereitung nach einem der Ansprüche 1 bis 6, dadurch gekennzeichnet, daß kein Komplexbildner enthalten ist.

8. Arzneimittelzubereitung nach einem der Ansprüche 1 bis 7, dadurch gekennzeichnet, daß kein Stabilisator enthalten ist.
9. Arzneimittelzubereitung nach einem der Ansprüche 1 bis 6, dadurch gekennzeichnet, daß ein Editinsäuresalz in einer Menge von größer 0 bis zu 25 mg/100 ml, bevorzugt von 5 bis kleiner 10 mg/100 ml enthalten ist.
10. Arzneimittelzubereitung nach Anspruch 9, dadurch gekennzeichnet, daß das Editinsäuresalz Natriumedetat ist.
11. Arzneimittelzubereitung nach einem der Ansprüche 1 bis 10, dadurch gekennzeichnet, daß der pH-Wert zwischen 2,5 und 3,5, bevorzugt zwischen 2,7 und 3,3 und ganz besonders bevorzugt zwischen 2,7 und 3,0 liegt.
12. Arzneimittelzubereitung nach einem der Ansprüche 1 bis 11, dadurch gekennzeichnet, daß die Konzentration an Tiotropium zwischen 0,0005 und 5 Gew.-%, bevorzugt bis zu 3 Gew.-% beträgt.
13. Arzneimittelzubereitung nach einem der Ansprüche 1 bis 12, dadurch gekennzeichnet, daß die Zubereitung Benzalkoniumchlorid als Konservierungsmittel enthält.
14. Arzneimittelzubereitung nach einem der Ansprüche 1 bis 6 und 9 bis 13, dadurch gekennzeichnet, daß Co-Solventien und/oder pharmakologisch akzeptablen Hilfs- und Zusatzstoffe neben dem Konservierungsmittel verwendet werden.
15. Arzneimittelzubereitung nach Anspruch 14, dadurch gekennzeichnet, daß die Zubereitung als Hilfsstoff ein Antioxidans enthält.
16. Arzneimittelzubereitung nach einem der Ansprüche 1 bis 15, dadurch gekennzeichnet, daß keine Co-Solventien und/oder pharmakologisch akzeptablen Hilfs- und Zusatzstoffe außer dem Konservierungsmittel verwendet werden.
17. Arzneimittelzubereitung nach einem der vorangegangenen Ansprüche, dadurch gekennzeichnet, daß die Konzentration an Tiotropium zwischen 0,001 und 3 Gew.-%, bevorzugt 0,0005 bis 0,5 Gew.-%, besonders bevorzugt 0,0005 bis 0,25 Gew.-% und besonders bevorzugt bei 0,001 bis 0,1 Gew.-% beträgt.
18. Arzneimittelzubereitung nach einem der vorangegangenen Ansprüche, dadurch gekennzeichnet, daß alle Bestandteile in dem Lösungsmittel gelöst sind.
19. Arzneimittelzubereitung nach einem der vorangegangenen Ansprüche, dadurch gekennzeichnet, daß der weitere Wirkstoff in dem Lösungsmittel suspendiert vorliegt.
20. Arzneimittelzubereitung nach einem der vorangegangenen Ansprüche, dadurch gekennzeichnet, daß der weitere Wirkstoff ein Steroid ist.
21. Arzneimittelzubereitung nach Anspruch 20, dadurch gekennzeichnet, daß die Konzentration des Steroids 0,05 bis 5 Gew.-%, bevorzugt 0,1 bis 2,5 Gew.-% beträgt.
22. Arzneimittelzubereitung nach einem der Ansprüche 20 oder 21, dadurch gekennzeichnet, daß Steroid Budesonid, Beclometasondipropionat, Fluticason und/oder Flunisolid ist.
23. Arzneimittelzubereitung nach einem der Ansprüche 1 bis 19, dadurch gekennzeichnet, daß der weitere Wirkstoff ein Antiallergikum und/oder ein Antihistaminikum ist.
24. Arzneimittelzubereitung nach Anspruch 23, dadurch gekennzeichnet, daß die Konzentration des Antiallergikums und/oder Antihistaminikums 0,05 bis 15 Gew.-% beträgt, bevorzugt bis 10 Gew.-%, stärker bevorzugt 0,1 bis 10 Gew.-%, besonders bevorzugt 0,1 bis 7 Gew.-%.
25. Arzneimittelzubereitung nach einem der Ansprüche 23 oder 24, dadurch gekennzeichnet, daß der weitere Wirkstoff Epinastin, Nedocromil, Dinatrumcromoglicat, Astemizol, Mequitazin, Carbinoxamin und/oder Clemastin und/oder ein entsprechendes pharmazeutisch akzeptables Salz davon ist.
26. Arzneimittelzubereitung nach einem der Ansprüche 1 bis 19, dadurch gekennzeichnet, daß der weitere Wirkstoff ein Leukotrienantagonist ist.
27. Arzneimittelzubereitung nach Anspruch 26, dadurch gekennzeichnet, daß die Konzentration des Leukotrienantagonisten 0,05 bis 10 Gew.-%, bevorzugt bis 5 Gew.-%, stärker bevorzugt 0,1 bis 3,5 Gew.-%. beträgt.
28. Arzneimittelzubereitung nach einem der Ansprüche 26 oder 27, dadurch gekennzeichnet, daß der Leukotrienantagonist Montelukast, Pranlukast, Zafirlukast, 1-(((R)-(3-(2-(6,7-Difluoro-2-chinolinyl)ethenyl)phenyl)-3-(2-(2-hydroxy-2-propyl)phenyl)thio)methylcyclopropanessigsäure, 1-(((R)-3-(3-(2-(2,3-dichlorothieno[3,2-b]pyridin-5-yl)-(E)-ethenyl)phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl)propyl)thio)methyl)cycloprpanessigsäure, [2-[[2-(4-tert-butyl-2-thiazolyl)-5-benzofuranyl]oxymethyl]phenyl]essigsäure ist.
29. Arzneimittelzubereitung nach Anspruch 1, enthaltend Wasser, ein oberflächenaktives Mittel, 0,1 Gew.-% Tiotropiumbromid, einen weiteren Wirkstoff aus der Gruppe der Antiallergika, Antihistaminika, Steroide und/oder Leukotrien-Antagonisten, 0,01 Gew.-% Benzalkoniumchlorid, 0,05 Gew.-% Natriumedetat, wobei die Zubereitung mit Salzsäure oder Zitronensäure auf einen pH-Wert von 3,0 eingestellt wird.
30. Arzneimittelzubereitung nach einem der Ansprüche 1 bis 29 zur Verwendung als Arzneimittel zur inhalativen Applikation.
31. Verwendung einer Arzneimittelzubereitung gemäß einem der Ansprüche 1 bis 29 zur Vernebelung in einem Inhalator gemäß der WO 91/14468 oder einem wie in den **Fig.** 6a und 6b der WO 97/12687 beschriebenen Inhalator.
32. Verwendung einer Arzneimittelzubereitung gemäß einem der Ansprüche 1 bis 29 zur Vernebelung in einem Inhalator, der definierte Mengen der Arzneimittelformulierung unter Anwendung von Drücken von 100 bis 600 bar durch eine Düse mit wenigstens einer Düsenöffnung mit einer Tiefe von 2 bis 10 Mikrometer und einer Breite von 5 bis 15 Mikrometern zu einem inhalierbaren Aerosol vernebelt.
33. Verwendung nach Anspruch 32, dadurch gekennzeichnet, daß die mindestens eine Düsenöffnung mindestens zwei Düsenöffnungen sind, die in Richtung der Düsenöffnung in einem Winkel von 20 Grad bis 160 Grad gegeneinander geneigt sind.
34. Verwendung nach Anspruch 32 oder 33, dadurch gekennzeichnet, daß die definierten Mengen 10 bis 50 Mikroliter betragen.
35. Verwendung nach einem der Ansprüche 31 bis 34, dadurch gekennzeichnet, daß der Inhalator eine Größe von 9 bis 15 cm in der Länge und 2 bis 4 cm in der Breite aufweist.

36. Verwendung nach einem der Ansprüche 31 bis 35, dadurch gekennzeichnet, daß die ausgebrachte Masse der Formulierung bei wenigstens 97% aller Betätigungen des Inhalators zwischen 5 und 30 mg mit einem Toleranzbereich von 25% liegt.

37. Verwendung nach einem der Ansprüche 31 bis 36, dadurch gekennzeichnet, daß die ausgebrachte Masse der Formulierung bei wenigstens 97% aller Betätigungen des Inhalators zwischen 5 und 30 mg mit einem Toleranzbereich von 20% liegt.

38. Verwendung nach einem der Ansprüche 36 oder 37, dadurch gekennzeichnet, daß die ausgebrachte Masse bei wenigstens 98% aller Betätigungen des Inhalators erreicht wird.

39. Verwendung einer Arzneimittelzubereitung nach einem der Ansprüche 1 bis 29 als Arzneimittel, insbesondere zur Behandlung von Asthma und/oder COPD.

40. Methode zur Behandlung von Asthma und/oder COPD unter Verwendung einer Arzneimittelzubereitung nach einem der Ansprüche 1 bis 29, insbesondere in einem Inhalator nach einem der Ansprüche 31 bis 38.

41. Verfahren zur Herstellung einer Arzneimittelzubereitung nach einem der Ansprüche 1 bis 29 durch Mischen der einzelnen Komponenten.

Hierzu 2 Seite(n) Zeichnungen

Nummer: DE 101 52 369 A1
Int. Cl.[7]: A 61 K 31/5365
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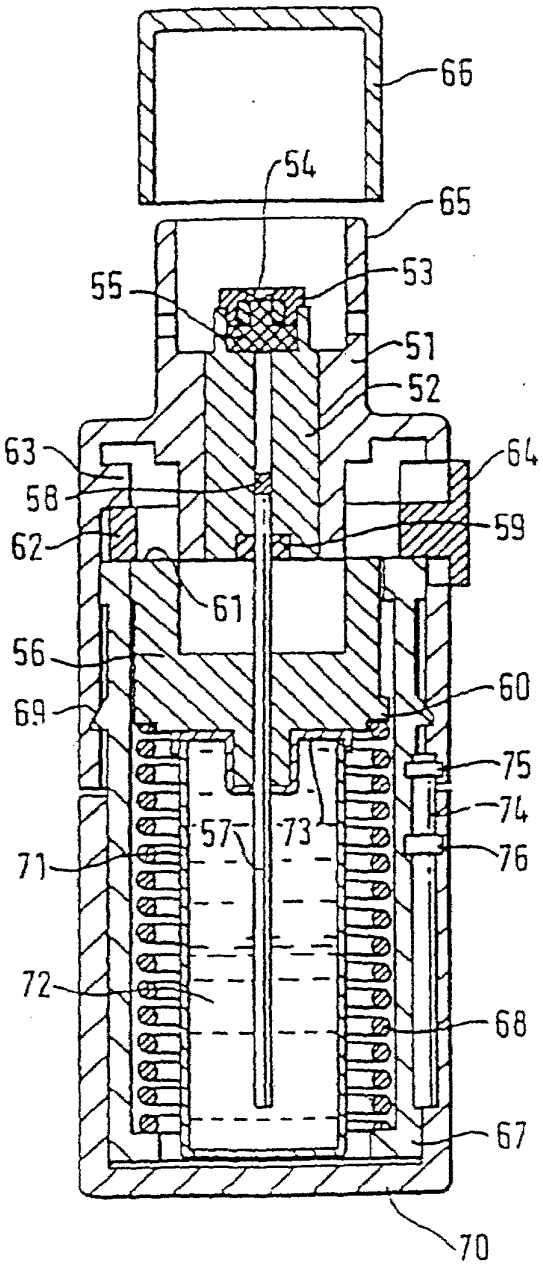

Fig. 1a

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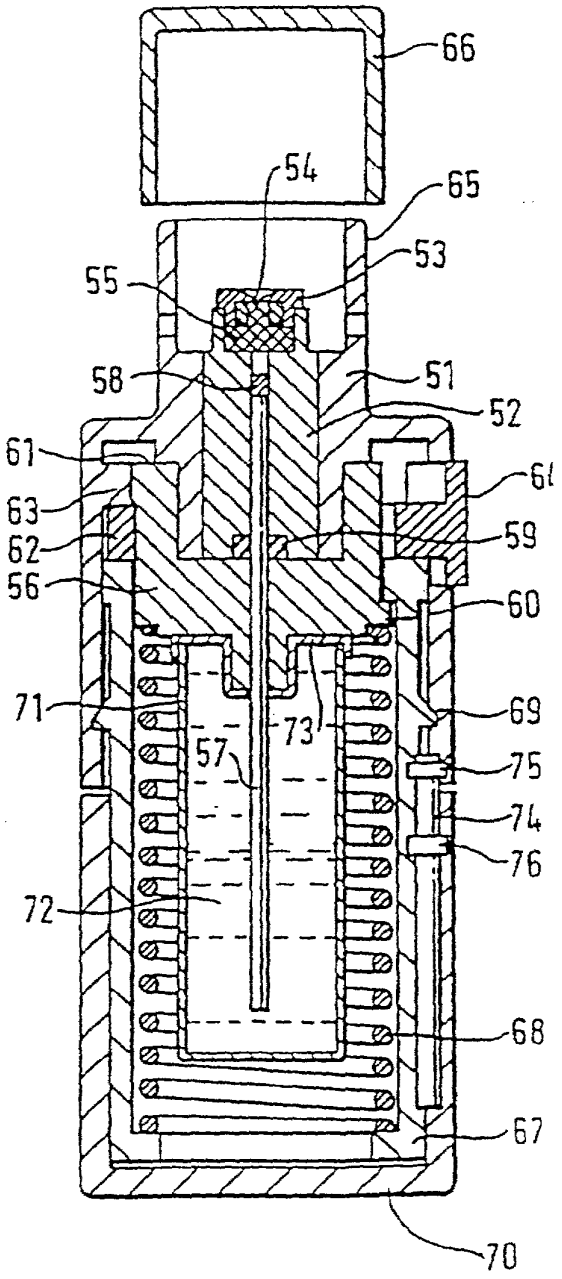

Fig. 1b

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(54) Title: A NASAL SPRAY CONTAINING AN INTRANASAL STEROID AND AN ANTIHISTAMINE

(57) Abstract

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, fluticasone, memetasone, budesonide, pharmaceutically acceptable salts thereof and mixtures thereof; b) a safe and effective amount of a fast acting antihistamine selected from the group consisting of acrivastine, carbinoxamine, diphenhydramine, chloropheniramine, brompheniramine, dexchloropheniramine, doxylamine, clemastine, promethazine, trimeprazine, methdilazine, hydroxyzine, pyrilamine, rocastine, tripelennamine, meclizine, tripolidine, azatadine, cyproheptadine, phenindamine, pharmaceutically acceptable salts thereof and mixtures thereof; and c) an aqueous, intranasal carrier wherein the composition is free of capsaicin and, preferably, free of powders or granules. The present invention also relates to a method for the treatment of symptoms associated with seasonal or perennial allergic rhinitis comprising the administration of a safe and effective amount of the intranasal pharmaceutical compositions of the present invention.

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A NASAL SPRAY CONTAINING AN INTRANASAL STEROID AND AN ANTIHISTAMINE

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 rhinitis. The symptoms of allergic rhinitis are nasal, ocular and palatial irritation, sneezing and hypersecretion. These symptoms occur following exposure to allergens. The main allergens are usually grass and/or tree pollens, hence, allergic rhinitis is common during the spring and summer months.

The symptoms of allergic rhinitis are believed to be due 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 rhinitis. Other forms of therapy include the use of cromolyn sodium, hypertonic salt solutions or immunotherapy.

Hagen et al., U.S. Patent 4,767,612, discloses nasal corticosteroid therapy as an effective means of treating allergic rhinitis; and is herein incorporated by reference. The effectiveness of these compounds is limited, however, by the slow onset of action characteristic of nasal corticosteroids (activity generally occurring anywhere from 1-3 days) and, occasionally, the occurrence of "break-through" symptoms. For similar reasons, such products also tend to limit consumer compliance.

Notwithstanding the many disclosures in the area of allergic rhinitis, there is still a need for additional formulations free of irritating powders or granules as well as irritating drugs such as capsaicin which provide fast and improved symptomatic relief with increased user acceptance and compliance.

The present inventor has found that by combining a nasal corticosteroid with a fast acting antihistamine, not only is the delay in onset considerably decreased, but the resulting compositions of the present invention also provide improved relief of those symptoms generally associated with either seasonal or perennial allergic rhinitis.

Additionally, combining the antihistamine with the nasal steroid results in improved symptom relief (e.g., improved nasal and ocular symptom relief). Furthermore, intranasal administration of antihistamines requires dosage amounts less than those associated with oral administration, thereby reducing potentially annoying side effects (e.g., drowsiness). By addressing such problems, the compositions of the present invention also help in improving overall patient compliance.

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 rhinitis.

Another object of the present invention is to provide an irritant free pharmaceutical composition for use in the treatment of symptoms generally associated with either seasonal or perennial allergic rhinitis.

A further object of the present invention is to provide a safe and effective method for treating seasonal or perennial allergic rhinitis.

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, fluticasone, memetasone, budesonide, pharmaceutically acceptable salts thereof and mixtures thereof;

b) a safe and effective amount of a fast acting antihistamine selected from the group consisting of acrivastine, carbinoxamine, diphenhydramine, chloropheniramine, brompheniramine, dexchloropheniramine, doxylamine, clemastine, promethazine, trimeprazine, methdilazine, hydroxyzine, pyrilamine, rocastine, tripelennamine, meclizine, triprolidine, azatadine, cyproheptadine, phenindamine pharmaceutically acceptable salts thereof and mixtures thereof; and

c.) an aqueous, intranasal carrier

wherein the composition is free of capsaicin and, preferably, free of powders or granules.

The present invention also relates to a method for the treatment of symptoms associated with seasonal or perennial allergic rhinitis comprising the administration of a safe and effective amount of the intranasal pharmaceutical compositions of the present invention.

By "symptoms associated with seasonal or perennial allergic rhinitis" is meant ocular and palatial irritation, 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 "fast acting," as used herein, refers to an onset of action which occurs within 15-30 minutes after administration.

The pH of the compositions is preferably from about 5 to about 9, more preferably from about 5.5 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 present invention are for nasal administration and contain a therapeutically safe and effective amount of the pharmaceutical agents described herein. 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, fluticasone, memetasone, 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 0.1%, more preferably from about 0.01% to about 0.1%.

Antihistaminic Agents

Antihistamines most useful to the present invention are histamine H-1 receptor antagonists which are fast acting. Such H-1 receptor antihistamines may be selected from among the following groups of antihistamines: alkylamines, ethanolamines, ethylenediamines, piperazines, phenothiazines, piperidines.

Examples of useful fast acting antihistamines include acrivastine, carbinoxamine, diphenhydramine, chloropheniramine, brompheniramine, dexchloropheniramine, doxylamine, clemastine, promethazine, trimeprazine, methdilazine, hydroxyzine, pyrilamine, tripelennamine, meclizine, triprolidine, azatadine, cyproheptadine, rocastine, phenindamine or pharmaceutically acceptable salts and mixtures thereof. Without being limited by theory, it is believed that the antihistamine additionally improves the delivery of the glucocorticoid, improving the glucocorticoid's onset of action. 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 3.0%, 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. Preferably, the nasal composition is isotonic, i.e., it has the same osmotic pressure as blood and lacrimal fluid. 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. Sodium chloride is preferred particularly for buffers containing sodium ions. Further examples of sodium choride equivalents are disclosed in Remington's Pharmaceutical Sciences pp. 1491-1497 (Alfonso Gennaro 18th ed. 1990), which is herein incorporated by reference.

Most preferred for use herein are aqueous, isotonic 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% and most preferably from about 0.5% to about 0.75%.

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 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 (preferable purified water) in addition to the antihistamine and glucocorticoid. Minor amounts of other ingredients such as pH adjusters (e.g., a base such as NaOH), emulsifiers or dispersing agents, buffering agents, preservatives, wetting agents and jelling agents (e.g., methylcellulose) may also be present.

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 needs, but it is suggested, as an example, that topical application range from about once per day to about three 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 50 mcg of the glucocorticoid agent and from about 5 mg to about 75 mg of the antihistaminic agent per dose (e.g., 50 mg to about 150 mg of the spray composition). A typical dose contains one to three sprays per nostril.

Optional Ingredients

An additional antihistamine may be optionally incorporated into the compositions of the present invention. Such antihistamines would preferably include those having a durations of action greater than 6 hours. Examples of such antihistamines include terfenadine, azelastine, cetirizine, astemizole, ebastine, ketotifen, lodoxamide, loratadine, levocabastine, mequitazine, oxatomide, setastine, tazifylline, temelastine or pharmaceutically acceptable salts and mixtures thereof. Active metabolites of the above antihistamines may also be used. Examples of such metabolites are disclosed in U.S. Patents 3,878,217 and 4,254,129, issued April 15, 1975 and March 3, 1981, respectively, to Carr et al.; U.S. Patent 5,375,693, issued December 27, 1994, to Woosley et al.; and European Patent 648759, each of which are herein incorporated by reference in their entirety.

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 a xanthine derivative such as caffeine and methylxanthine and the like. The xanthine derivative may preferably be incorporated at concentrations of from about 0.01% to about 1%, most preferably from about 0.1% to about 0.5. Mixtures of xanthine derivatives may also be incorporated.

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, ketorolac, flurbiprofen, indomethacin, ketoprofen, naproxen, pharmaceutically-acceptable salts thereof, optically active racemates thereof and mixtures thereof. Preferred for use herein are the S(+) isomers of the nonopiate analgesics. 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.

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 Zafirlukast (Accolate, Zeneca), MK-571 (Merck, Sharp and Dohme), 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 European Patent Application 318093, and Fleisch, J. H., Development of Cysteinyl Leukotriene Receptor Antagonists, Vol. 12 Advances in Inflammation Research 173-189 (A. Lewis et al. ed. 1988), Both of which are herein incorporated by reference in their entirety.

Lipoxygenase inhibiting compounds may also be incorporated into the compositions of the present invention. Suitable examples are discussed in U.S. Patent 4,873,259, to Summers et al., issued October 10 1989 and U.S. Patent 5,037,853, to Brooks et al., issued August 6, 1991, both of which are herein incorporated by reference in their 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.

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 cellulose, chitosan, 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.

Combinations of any of the above optional components may also be incorporated.

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, preservatives for maintaining the antimicrobial integrity of the compositions, 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 and the above ingredient 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
chlorpheniramine	0.500
avicel RC - 591[1]	1.200
dextrose	5.100
polysorbate 80	0.050
benzalkonium chloride	0.020
phenylethyl alcohol	0.025
distilled water	q.s. 100ml

[1]microcrystalline cellulose and sodium carboxymethyl cellulose, supplied FMC Corporation.

In an appropriately sized vessel, the above listed ingredients are added one at a time to water with mixing, allowing each to dissolve before adding the next. After all the ingredients have been added, purified water is used to bring the batch to the appropriate weight.

Administration of approximately 0.5 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
chlorpheniramine	0.350
levocabastine	0.0125
propylene glycol	2.000
polyethylene glycol	1.000
ethylenediamine tetraacetic acid	0.050

benzalkonium chloride	0.010
distilled water	q.s. 100ml

The above ingredients are combined

Administration of approximately 0.5 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
acrivastine HCl	0.100
polysorbate 80	0.050
glycerin	2.000
hydroxypropyl methyl cellulose	1.000
ethylenediamine tetraacetic acid	0.050
benzalkonium chloride	0.020
distilled water	q.s. 100ml

Administration of approximately 0.5 grams of the composition is used for topical nasal application to provide relief from allergy or allergy-like symptoms.

Example IV

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 %**
beclomethasone diproprionate, monohydrate	0.042
chlorpheniramine	0.500
oxymetazoline	0.050
avicel RC - 591[1]	1.200
dextrose	5.100
polysorbate 80	0.050
benzalkonium chloride	0.020
phenylethyl alcohol	0.025
distilled water	q.s. 100ml

[1]microcrystalline cellulose and sodium carboxymethyl cellulose, supplied FMC corporation.

Administration of approximately 0.5 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 or by using, in whole or in part, equivalent amounts of other fast acting antihistamines such as carbinoxamine, diphenhydramine, brompheniramine, dexchloropheniramine, doxylamine, clemastine, promethazine, rocastine, trimeprazine, methdilazine, hydroxyzine, pyrilamine, tripelennamine, meclizine, triprolidine, azatadine, cyproheptadine, phenindamine, pharmaceutically acceptable salts thereof and mixtures thereof. Furthermore, the above described compositions may also contain a sympathomimetic amine such as pseudoephedrine, phenylpropanolamine, phenylephrine, tetrahydrozoline, naphazoline, oxymetazoline, tramazoline, 5-(2-imidazolinylamino)benzimedazoles, 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.

What is claimed is:

1. A pharmaceutical composition comprising:
   a) a safe and effective amount of a glucocorticoid selected from the group consisting of beclomethasone, flunisolide, fluticasone, memetasone, budesonide, pharmaceutically acceptable salts thereof and mixtures thereof;
   b) a safe and effective amount of a fast acting antihistamine selected from the group consisting of acrivastine, carbinoxamine, diphenhydramine, chloropheniramine, brompheniramine, dexchloropheniramine, doxylamine, clemastine, promethazine, rocastine, trimeprazine, methdilazine, hydroxyzine, pyrilamine, tripelennamine, meclizine, triprolidine, azatadine, cyproheptadine, phenindamine, pharmaceutically acceptable salts thereof and mixtures thereof; and
   c) an aqueous, intranasal carrier

   wherein the composition is free of capsaicin.

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 beclomethasone.

4. A pharmaceutical composition according to any one of the preceding Claims, which further comprises a sympathomimetic amine selected from the group consisting of pseudoephedrine, phenylpropanolamine, phenylephrine, tetrahydrozoline, naphazoline, oxymetazoline, tramazoline, pharmaceutically acceptable salts thereof and mixtures thereof.

5. A pharmaceutical compositions according to any one of the preceding Claims, which further comprises an additional antihistamine selected from the group consisting of terfenadine, azelastine, cetirizine, astemizole, ebastine, ketotifen, lodoxamide, loratadine, levocabastine, mequitazine, oxatomide, setastine, tazifylline, temelastine or pharmaceutically acceptable salts and mixtures thereof.

6. A pharmaceutical composition according to any one of the preceding Claims, which further comprises a non-steroidal anti inflammatory agent.

7. A pharmaceutical composition according to any one of the preceding Claims, which further comprises a lipoxygenase inhibitor or antagonist.

8. A pharmaceutical composition according to any one of the preceding Claims, which further comprises a nonopiate analgesic.

9. A method for treatment of seasonal allergic rhinitis or using a safe and effective amount of the composition of any one of the preceding Claims.

10. A method for treatment of perennial allergic rhinitis using a safe and effective amount of the composition of any one of the preceding Claims.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/57 A61K31/56 A61K31/44 A61K31/445 A61K31/415
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B. FIELDS SEARCHED

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

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 97 01337 A (MCNEIL PPC INC) 16 January 1997 * see the whole application * ---	1-3
Y	INT. J. PEDIAT. OTORHINOLARYN., vol. 3, no. 4, 1981, pages 287-294, XP002040649 BUSINCO ET AL.: "Clinical and therapeutic aspects of sinusitis in children with bronchial asthma" * see summary, Table VII * --- -/--	1-4

[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

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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	J. ALLERG. CLIN. IMMUNOL., vol. 79, no. 6, 1987, pages 887-892, XP002040650 VANZIELEGHEM ET AL. : "A comparison of budesonide and beclomethasone dipropionate nasal aerosols in ragweed-induced rhinitis" * see the abstract, Fig. 4 *	1-4
Y	ALLERGY ASTHMA PROC, vol. 17, no. 3, 1996, pages 149-156, XP002040651 RATNER ET AL.: "New formulation of aqueous flunisolide nasal spray in the treatment of allergic rhinitis: comparative assessment of safety, tolerability, and efficacy" *see the abstract *	1-4
P,Y	WO 97 01341 A (MCNEIL PPC INC) 16 January 1997 * see claim 1 *	1-3
E	EP 0 780 127 A (PROCTER & GAMBLE) 25 June 1997 * see claim 1; page 3, lines 24-30 *	1

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 97/09518

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9701337 A	16-01-97	AU 6392496 A	30-01-97
WO 9701341 A	16-01-97	AU 6290396 A	30-01-97
EP 0780127 A	25-06-97	NONE	

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(56) Related Art
Busse W et al (1996). American Journal of Respiratory and Critical Care Medicine. Vol 153,1:122-127
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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.

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(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.

2003244799 13 Aug 2009

PHARMACEUTICAL PRODUCTS AND FORMULATIONS

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 ciclesonide. 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.

While it is described that aspects of the present invention involve the use of steroids such as beclomethasone, mometasone, fluticasone, budesonide and ciclesonide, the present invention particularly relates to fluticasone or a pharmaceutically acceptable ester thereof.

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 ciclesonide, 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)

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In the claims which follow and in the preceding description of the invention, except where the context requires otherwise due to express language or necessary implication, the word "comprise" or variations such as "comprises" or "comprising" is used in an inclusive sense, i.e. to specify the presence of the stated features but not to preclude the presence or addition of further features in various embodiments of the invention.

It is to be understood that, if any prior art publication is referred to herein, such reference does not constitute an admission that the publication forms a part of the common general knowledge in the art, in Australia or any other country.

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THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. 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.

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

3. A formulation according to claim 1 or 2, wherein said fluticasone or a pharmaceutically acceptable ester thereof is present as fluticasone propionate or fluticasone valerate.

4. A formulation according to any of claims 1 to 3, which contains said fluticasone or a pharmaceutically acceptable ester thereof in an amount from about 50 micrograms/ml to about 5 mg/ml of the formulation.

5. A formulation according to any of claims 1 to 4, wherein the formulation has a particle size of less than about 10 μm, or less than 5 μm.

6. A formulation according to any of claims 1 to 5, which also contains a surfactant, comprising a polysorbate or poloxamer surfactant.

7. A formulation according to claim 6, which contains from about 50 micrograms to about 1 milligram of surfactant per ml of the formulation.

8. A formulation according to any of claims 1 to 7, which also contains an isotonic agent comprising sodium chloride, saccharose, glucose, glycerine, sorbitol or 1,2-propylene glycol.

9. A formulation according to any of claims 1 to 8, which also contains at least one of a buffer, a preservative, and a suspending or thickening agent, wherein said

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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, or 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, or wherein the buffer comprises a citric acid-citrate buffer.

10. A formulation according to claim 9, wherein the buffer maintains the pH of the aqueous phase at from about 3 to about 7, or from about 4.5 to about 6.5.

11. A formulation according to any of claims 1 to 10, which is in a form suitable for nasal or ocular administration.

12. A formulation according to any of claims 1 to 11, which is an aqueous suspension or solution.

13. A formulation according to any of claims 1 to 12, which is a suspension containing from 0.0005 to 2% (weight/weight of the formulation) of said azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, and from 0.5 to 1.5% (weight/weight of the formulation) of said fluticasone, or a pharmaceutically acceptable ester thereof, or from 0.001 to 1% (weight/weight of the formulation) of said azelastine, solvate or physiologically functional derivative thereof, and from 0.5% to 1.5% (weight/weight of the formulation) of said fluticasone, or a pharmaceutically acceptable ester thereof.

14. A formulation according to any of claims 1 to 13, which is in the form of an aerosol, an ointment, eye drops, nasal drops, a nasal spray, or an inhalation solution.

15. A formulation according to claim 14, which is in the form of nasal drops or nasal spray, or which is in the form of an aerosol.

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16. A formulation according to any of claims 1 to 15 which is in the form of an insufflation powder.

17. A formulation according to any of claims 1 to 16, which comprises azelastine hydrochloride and fluticasone propionate.

18. A formulation according to any of claims 1 to 16, which comprises azelastine hydrochloride and fluticasone valerate.

19. Use of a pharmaceutical formulation as defined in any of claims 1 to 18 in the preparation of a medicament for the treatment of seasonal or perennial allergic rhinitius, or seasonal or perennial allergic conjunctivitis.

20. Use according to claim 19, wherein the medicament for the treatment of seasonal or perennial allergic rhinitius is in the form of a nasal spray.

21. Use according to claim 19, wherein the medicament for medicament for the treatment of seasonal or perennial allergic conjunctivitis is in the form of eye drops.

22. A method of treating seasonal or perennial allergic rhinitius, or seasonal or perennial allergic conjunctivitis, comprising administering an effective amount of a pharmaceutical formulation as defined in any of claims 1 to 18 to a subject in need thereof.

23. A method according to claim 22, wherein the pharmaceutical formulation is in the form of a nasal spray when used for the treatment of seasonal or perennial allergic rhinitius.

24. A method according to claim 22, wherein the pharmaceutical formulation is in the form of eye drops when used for the treatment of seasonal or perennial allergic conjunctivitis.

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25. A pharmaceutical formulation as defined in claim 1, or uses and methods involving the pharmaceutical formulation, substantially as herein described with reference to any of Examples 1, 3, 4, 5, 9, 10, 11, 12, 13 and 14.

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(72)Inventor : NAKAJIMA NOBORU

(54) PHARMACEUTICAL COMPOSITION FOR ALLERGIC DISEASE

(57)Abstract:
PROBLEM TO BE SOLVED: To provide a pharmaceutical composition for allergic disease, truly effective for prophylaxis, mitigation or amelioration of the allergic disease, and not causing anxiety of side effects.
SOLUTION: This pharmaceutical composition for the allergic disease contains a steroid drug, an antihistaminic agent and licorice.

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(54)【発明の名称】　アレルギー性疾患用医薬組成物

(57)【要約】
【課題】本発明は、アレルギー性疾患の予防、緩和もしくは改善に対し真に有効で、かつ副作用の懸念のないアレルギー性疾患用医薬組成物を提供することを目的とする。
【解決手段】ステロイド剤、抗ヒスタミン剤およびカンゾウを含有してなるアレルギー性疾患用医薬組成物。

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【特許請求の範囲】

【請求項１】　ステロイド剤、抗ヒスタミン剤およびカンゾウを含有してなるアレルギー性疾患用医薬組成物。

【請求項２】　ステロイド剤がデキサメタゾンであり、抗ヒスタミン剤がマレイン酸クロルフェニラミンである．請求項１記載の組成物。

【請求項３】　さらに、牡蠣を含有してなる請求項１または２記載の組成物。

【請求項４】　さらに、キジツ、キキョウ、オウレン、オウバク、サンシシ、オウゴンおよびトウキからなる群より選ばれる少なくとも１種を含有してなる、アトピー性皮膚炎のための請求項１～３いずれか記載の組成物。

【請求項５】　さらに、マオウ、ブシ．サイシン．カンキョウ、レンギョウおよびシンイからなる群より選ばれる少なくとも１種を含有してなる、アレルギー性鼻炎または花粉症のための請求項１～３いずれか記載の組成物。

【請求項６】　さらに、ハンゲ、バクモンドウ．サイシン．カンキョウ．ゴミシおよびキキョウからなる群より選ばれる少なくとも１種を含有してなる、アレルギー性気管支炎または喘息のための請求項１～３いずれか記載の組成物。

【発明の詳細な説明】

【０００１】

【発明の属する技術分野】本発明は．アレルギー性疾患用医薬組成物に関する。

【０００２】

【従来の技術】近年、アレルギー性疾患の罹患者数は増加の一途を辿っており、特に花粉症とアトピー性皮膚炎の罹患者の増加は著しいものがある。抗原の増加のみならず．大気汚染や食品添加物．食生活の変化といった周囲の環境の変化が、アレルギーの増加の原因であると推定されている。

【０００３】アレルギー性疾患は外部抗原に対する生体側の過剰防衛反応であり．抗体産生細胞等の過剰対応が原因であるとされている。すなわち．人体の持つ抵抗力の過剰反応ということができる。

【０００４】このようなアレルギー性疾患の治療では、従来．抗ヒスタミン剤やステロイド剤等の投与が対症療法的に行われてきた。しかしながら．これらの薬剤を用いても充分な効果は得られず、また副作用が強く．安全性の点でも問題があった。

【０００５】

【発明が解決しようとする課題】本発明は、アレルギー性疾患の予防．緩和もしくは改善に対し真に有効で、かつ副作用の懸念のないアレルギー性疾患用医薬組成物を提供することを目的とする。

【０００６】

【課題を解決するための手段】本発明者は鋭意検討した結果．ステロイド剤、抗ヒスタミン剤およびカンゾウを

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含有してなる組成物が所望の効果を発現し得ることを見出し．本発明を完成するに至った。

【０００７】即ち、本発明は、（１）　ステロイド剤、抗ヒスタミン剤およびカンゾウを含有してなるアレルギー性疾患用医薬組成物、（２）　ステロイド剤がデキサメタゾンであり．抗ヒスタミン剤がマレイン酸クロルフェニラミンである、前記（１）記載の組成物、（３）　さらに、牡蠣を含有してなる前記（１）または（２）記載の組成物、（４）　さらに、キジツ．キキョウ．オウレン．オウバク．サンシシ．オウゴンおよびトウキからなる群より選ばれる少なくとも１種を含有してなる、アトピー性皮膚炎のための前記（１）～（３）いずれか記載の組成物、（５）　さらに、マオウ．ブシ、サイシン．カンキョウ．レンギョウおよびシンイからなる群より選ばれる少なくとも１種を含有してなる、アレルギー性鼻炎または花粉症のための前記（１）～（３）いずれか記載の組成物．ならびに（６）　さらに、ハンゲ、バクモンドウ、サイシン、カンキョウ．ゴミシおよびキキョウからなる群より選ばれる少なくとも１種を含有してなる．アレルギー性気管支炎または喘息のための前記（１）～（３）いずれか記載の組成物．に関する。

【０００８】

【発明の実施の形態】本発明にいう「抗アレルギー」とは．あらゆるアレルギー性疾患の予防．緩和もしくは改善に機能し得るということを意図するものである。また．「改善」とは治療の意を含むものである。

【０００９】前記アレルギー性疾患とは、一般に．アレルギー、即ち免疫反応の病的過程の結果生ずる疾患であると定義されている。アレルギーは．その発症機序からＩ型．ＩＩ型．ＩＩＩ型とＩＶ型とに分類されている。Ｉ型はＩｇＥクラスの抗体．ＩＩ型はＩｇＧおよびＩｇＭクラスの抗体．ＩＩＩ型は免疫複合体、ＩＶ型は感作リンパ球が、それぞれ特異的な免疫反応因子である。例えば．Ｉ型アレルギー反応には気管支炎、喘息．花粉症．結草熱、蕁麻疹、アレルギー性鼻炎や昆虫アレルギーが．ＩＩ型アレルギー反応には血液型不適合溶血性貧血．アレルギー性血小板．白血球減少症、グッドパスチャー症候群等が．ＩＩＩ型アレルギー反応にはアルサス反応．血清病．各種糸球体腎炎等が．ＩＶ型アレルギー反応には接触性皮膚炎、ツベルクリン反応が挙げられる。また、遺伝的素因による傾向が強い、アトピー性皮膚炎やアトピー性鼻炎等のアトピー性疾患も含まれる。

【００１０】本発明においては、なかでも、アレルギー性鼻炎、アレルギー性気管支炎、喘息．花粉症およびアトピー性皮膚炎からなる群より選ばれる少なくとも１種の予防、緩和もしくは改善に該組成物を使用するのが好ましい。

【００１１】また、本発明の組成物は．アレルギー性疾患として他に．原発の諸症状の予防．緩和もしくは改善に対しても有効であり、例えば、風邪に伴う炎症．のど

のはれ、せき、鼻汁、鼻づまり等の予防、緩和もしくは改善に該組成物を使用するのが好ましい。

【００１２】本発明の組成物は、ステロイド剤、抗ヒスタミン剤およびカンゾウを含有してなることに１つの大きな特徴を有しており、具体的な作用機序は未だ明らかではないが、個々の成分の効果が相乗的に高められることから、抗アレルギー作用が有意に増強されるものと推定される。

【００１３】前記ステロイド剤としては、たとえば、酢酸コルチゾン、ヒドロコルチゾン、コハク酸ヒドロコルチゾンナトリウム、プレドニゾロン、メチルプレドニゾロン、コハク酸メチルプレドニゾロンナトリウム、トリアムシノロン、トリアムシノロンアセトニド、デキサメタゾン、パルミチン酸デキサメタゾン、ベタメタゾン、酢酸パラメタゾン、酢酸フルドロコルチゾン、酢酸ハロプレドン等を挙げることができる。これらは、単独でまたは２種以上混合して用いることができる。なかでも、本発明の所望の効果を得る観点からデキサメタゾンが好ましい。

【００１４】前記デキサメタゾンとは強力な抗炎症、抗アレルギー作用を持つ合成グルココルチコイドであり、従来、膠原病、気管支炎、喘息、アトピー性疾患等の難治性の疾患の治療に用いられている薬剤である。しかしながら、胃潰瘍、副腎萎縮等の重篤な副作用を発現することが知られており、使用の制限がある。本発明の組成物においては、個々の成分の相乗効果により、副作用の懸念のない使用範囲で充分にその作用効果を発現させることが可能である。デキサメタゾンは、例えば、市販のものを粉末にして使用すればよい。

【００１５】前記抗ヒスタミン剤としては、エタノールアミン系とプロピルアミン系のものが好ましく、たとえば、エタノールアミン系のものとしては、ジフェンヒドラミン、塩酸ジフェニルピラリン、テオクル酸ジフェニルピラリン、フマル酸クレマスチン、ジメンヒドリナート等が挙げられ、プロピルアミン系のものとしては、マレイン酸クロルフェニラミン等を挙げることができる。これらは、単独でまたは２種以上混合して用いることができる。なかでも、本発明の所望の効果を得る観点からプロピルアミン系のものが好ましく、さらにマレイン酸クロルフェニラミンが特に好ましい。

【００１６】前記マレイン酸クロルフェニラミンは、従来、風邪薬として用いられている薬剤であり、例えば、市販のものを使用することができる。

【００１７】前記カンゾウとは、鎮痛、鎮咳等の作用を有する漢方薬であり、種々の症状の治療に用いられている薬剤である。なお、カンゾウは古くから用いられており、安全性に関しての懸念は極めて少ない。カンゾウは、その乾燥物をそのまま用いることができる。

【００１８】本発明の組成物における各成分の含有量としては、ステロイド剤が好ましくは５～１０重量%、より好ましくは６～９重量%、抗ヒスタミン剤が好ましくは２０～６０重量%、より好ましくは３０～５０重量%、カンゾウが好ましくは５～５０重量%、より好ましくは１０～４０重量%である。

【００１９】本発明の組成物においては、前記３成分に加えさらに牡蠣を含有させるのが好ましい。

【００２０】前記牡蠣とは、かきの貝殻を焼いて製した粉末である。鎮静、鎮痙、収斂、解熱等の作用を有する漢方薬であり、従来、顔面紅潮、頭部の熱感、不眠、動悸、発熱疾患後の微熱などで体の衰弱がある者等の治療に用いられている薬剤である。なお、牡蠣は古くから用いられており、安全性に関しての懸念は極めて少ない。

【００２１】前記カンゾウ同様、牡蠣についても、乾燥物を用いることができる。

【００２２】本発明の組成物における牡蠣の含有量としては、好ましくは５～２０重量%、より好ましくは１０～１５重量%である。

【００２３】また本発明の組成物においては、さらに、【１】キジツ、キキョウ、オウレン、オウバク、サンシシ、オウゴンおよびトウキからなる群より選ばれる少なくとも１種を用いることが、アトピー性皮膚炎の予防、緩和もしくは改善の観点から好ましい。これらの成分は古くから用いられている漢方薬であり、抗炎症、抗菌、抗ウイルス、抗真菌等の作用を有することが知られている。また、安全性に関する懸念も極めて少ない。前記カンゾウ同様、これらの成分についても、乾燥物を用いることができる。

【００２４】また同様に、本発明の組成物においては、さらに、【２】マオウ、ブシ、サイシン、カンキョウ、レンギョウおよびシンイからなる群より選ばれる少なくとも１種を用いることが、アレルギー性鼻炎または花粉症の予防、緩和もしくは改善の観点から好ましい。これらの成分は古くから用いられている漢方薬であり、循環促進、健胃、抗菌、消炎、抗ウイルス、利尿等の作用を有することが知られている。また、安全性に関する懸念も極めて少ない。前記カンゾウ同様、これらの成分についても、乾燥物を用いることができる。

【００２５】また同様に、本発明の組成物においては、さらに、【３】ハンゲ、バクモンドウ、サイシン、カンキョウ、ゴミンおよびキキョウからなる群より選ばれる少なくとも１種を用いることが、アレルギー性気管支炎または喘息の予防、緩和もしくは改善の観点から好ましい。これらの成分は古くから用いられている漢方薬であり、去痰、鎮咳、抗菌、消炎、鎮静等の作用を有することが知られている。また、安全性に関する懸念も極めて少ない。前記カンゾウ同様、これらの成分についても、乾燥物を用いることができる。

【００２６】これらの各症状に合わせて用いることが好ましい漢方薬〔１〕～【３】として列挙する成分の本発明の組成物における含有量は、所望の効果が得られるよ

うに適宜調節すればよいが、例えば、かかる成分の合計量は〔１〕～〔３〕のいずれの群においても好ましくは５～１５重量%、より好ましくは５～１０重量%である。

【００２７】本発明の組成物の剤型は特に限定されるものではなく、前記例示した各成分のみを単に混和して、あるいは一般に製剤上許容され得る１種以上のベヒクル、担体、賦形剤、結合剤、防腐剤、安定剤、矯味矯臭剤、コーティング剤、着色剤、糖衣剤、崩壊剤、増量剤、滑沢剤等と共に混和して、粉末剤、錠剤、散剤、顆粒剤、カプセル剤、水薬等の経口投与剤とすることができ、特に粉末剤が好ましい。これらは、前記各成分を配合する以外は、従来公知の技術を用いて製造することができる。

【００２８】このような本発明の組成物の好適な投与量＊は、疾患の種類、症状、患者の年令、性別、体重等により異なるが、成人１人１日当たり、２０００～３５００ｍｇが適当である。

【００２９】本発明の組成物は、あらゆるアレルギー性疾患の予防、緩和もしくは改善に有効であり、アレルギー性疾患の治療薬もしくは化粧料等として用いることができる。

【００３０】

【実施例】以下、本発明を実施例により具体的に説明するが、本発明は実施例のみに限定されるものでない。

【００３１】実施例１

表１の配合〔（１）～（４）〕に従って常法により各成分を混合し粉末剤を得た。

【００３２】

【表１】

成人（１人当たり）１日分処方（薬剤３５００ｍｇを１日に３回に分けて投与）

成分	配合量（重量%）			
	（１）	（２）	（３）	（４）
デキサメタゾン	７．２	７．２	６．５	７．２
マレイン酸クロルフェニラミン	３２．０	２２．６	３２．６	３２．０
カンゾウ	３２．０	１５．６	１４．７	１５．０
竹茹	１５．８	－	－	９．４
キジツ	７．８	７．８	７．８	－
キキョウ	７．８	－	７．８	－
トウキ	－	－	－	７．８
マオウ	－	７．８	－	－
ブシ	－	７．８	－	７．８
サイシン	－	７．８	－	７．８
カンキョウ	－	７．６	７．８	７．８
レンギョウ	－	７．８	－	－
シンイ	－	７．６	－	－
ハンゲ	－	－	７．８	－
バクモンドウ	－	－	７．８	－
ゴミシ	－	－	７．８	７．８

【００３３】実施例２

常法に従い、前記表１の配合〔（１）～（４）〕に従う各成分と適当量の乳糖およびステアリン酸マグネシウムとを混合し、この混合物を単発式打錠機にて打錠し、錠剤を製造する。

【００３４】実施例３

実施例２で得た錠剤を粉砕、製粒し、篩別して顆粒剤を製造する。

【００３５】治療例１

以下に示す治療例は、基本的に病院で６ヵ月以上治療して改善の認められなかった患者を対象としたものである。

【００３６】（１）アトピー性皮膚炎

３４才男性。表１の（１）に示す薬剤を１日３回、７日間投与した時点で痒み、赤味の軽減がみられ、２８日位でほとんど消失した。以後、自覚症状に応じて頓服的に薬剤を投与し、予防、治療に努めている。

【００３７】（２）アレルギー性鼻炎

５８才男性。長年アレルギー性鼻炎の症状で、もう治らないとあきらめていた患者。表１の（２）に示す薬剤を１日３回、１４日間投与した時点で症状はほとんど消失したが、元の症状の再発を恐れ、現在も頓服的に使用し

ている。風邪をひきやすかったが、現在は風邪もひかなくなり、体調良好である。

【００３８】（３）アレルギー性気管支炎

５４才女性。季節変わりに必ずのどがいがらっぽくなり．咳がとまらなくなる患者。表１の（３）に示す薬剤を１日３回、７日間投与した時点で症状が軽減し．１４日位でほとんど消失した。現在は季節変わりに１日１回（１／３量）で予防的に使用している。

【００３９】（４）喘息

５９才男性。長年喘息で苦しみ、夜も眠れないことがあった患者。表１の（３）に示す薬剤を１日３回．１０日間投与した時点で緩解がみられ、３０日位で消失した。以後．１日２回（２／３量）で３０日．１日１回（１／＊３量）で３０日と減量し．調子によって自分で加減して継続して使用している。前記（２）の患者と同様に風邪をひきにくくなった。

【００４０】（５）花粉症

５２才女性。毎年２月下旬から症状が出るので．同じ時期に必ず来局する患者。表１の（２）に示す薬剤を１日１回（１／３量）の投与で鼻水、鼻づまりなどの症状が軽減した。

【００４１】

【発明の効果】本発明により、副作用の懸念なく効果的にアレルギー性疾患の予防．緩和もしくは改善を行うことができるアレルギー性疾患用医薬組成物が提供される。

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