EXHIBIT 1005(A)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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

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

CERTIFICATE OF EFS-WEB FILING

I hereby certify that this correspondence is being electronically filed at the USPTO website to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria VA 22313-1450 on 7/23/2009

Edith Shek

Edith S. Shek

AMENDMENTS AND RESPONSE TO
OFFICE ACTION DATED JANUARY 23, 2009

Dear Sir:

In response to the Office Action dated January 23, 2009, Applicants respectfully request the following amendments to the above-identified application as follows. The changes made are shown by underlining the added text and striking through the deleted text.

Amendments to the Claims are reflected in the listing of claims, which begins on page 2 of this paper.

Remarks/Arguments begin on page 10 of this paper.

AMENDMENTS TO THE CLAIMS

Listing of Claims:

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

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

3. (Canceled)

4. (Currently Amended) A formulation according to ~~claim 3~~claim 1, wherein the ~~steroid~~ pharmaceutically acceptable ester is ~~beclomethasone propionate, mometasonefuroate, mometasone furoate monohydrate,~~ fluticasone propionate or fluticasone valerate.

5. (Canceled)

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

7. (Currently Amended) A formulation according to claim 1, which is a suspension containing 0.0005 to 2% (weight/weight of the formulation) of azelastine or a pharmaceutically acceptable salt of azelastine, and from 0.5 to 1.5% (weight/weight of the formulation) of fluticasone or a pharmaceutically acceptable ester thereof~~said steroid~~.

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

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

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

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

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

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

14. (Previously Presented) A formulation according to claim 1, which also contains at least one additive selected from the group consisting of a buffer, a preservative, a suspending agent and a thickening agent.

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

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

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

18. (Currently Amended) A formulation according to claim 14, wherein the buffer maintains the pH of the aqueous phase at from 3 to 7~~, preferably 4.5 to about 6.5~~.

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

20. (Previously Presented) A formulation according to claim 1, which is in the form of an aerosol, an ointment, eye drops, nasal drops, a nasal spray, an inhalation solution and other forms suitable for nasal or ocular administration.

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

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

23-24. (Canceled)

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

26. (Currently Amended) A pharmaceutical product~~ according to claim 1~~, comprising (i) azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, provided in an aerosol formulation preferably together with a propellant typically suitable for MDI delivery, and (ii) fluticasone or a pharmaceutically acceptable ester thereof~~at least one steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative~~

~~thereof~~, provided in an aerosol formulation preferably together with a propellant typically suitable for MDI delivery, as a combined preparation for simultaneous, separate or sequential use in the treatment of conditions for which administration of one or more anti-histamine and/or one or more steroid is indicated.

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

28. (Currently Amended) A pharmaceutical product comprising (i) azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, provided as an insufflation powder, and (ii) fluticasone or a pharmaceutically acceptable ester thereof~~at least one steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof~~, provided as an insufflation powder, as a combined preparation for simultaneous, separate or sequential use in the treatment of conditions for which administration of one or more anti-histamine and/or one or more steroid is indicated.

29. (Currently Amended) An insufflation powder formulation comprising (i) azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, and (ii) fluticasone or a pharmaceutically acceptable ester thereof~~at least one steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof~~, together with a pharmaceutically acceptable carrier or excipient therefor.

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

31-34. (Canceled)

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

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

37. (Currently Amended) A pharmaceutical product comprising the pharmaceutical formulation of claim 1, wherein said azelastine is azelastine hydrochloride and said pharmaceutically acceptable ester~~steroid~~ is fluticasone valerate, as a combined preparation for

simultaneous, separate or sequential use in the treatment of conditions for which administration of one or more anti-histamine and/or one or more steroid is indicated.

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

39-43. (Canceled)

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

45. (Currently Amended) A process of preparing a pharmaceutical formulation according to claim 1, which process comprises admixing a pharmaceutically acceptable carrier or excipient with azelastine, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, and fluticasone or a pharmaceutically acceptable ester thereof~~at least one steroid, or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof~~.

46-52. (Canceled)

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

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

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

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

REMARKS/ARGUMENTS

Status of Claims

Claims 1, 4, 6, 7, 8, 18, 26, 28, 29, 30, 35, 36, 37, 38, 44, and 45 have been amended.

Claims 3, 5, 23-24, 31-34, 39-43, and 46-52 have been canceled.

New claims 53-56 have been added.

Thus, claims 1, 2, 4, 6-22, 25-30, 35-38, 44-45, and 53-56 are currently pending in this application.

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

Restriction Requirement

Applicants affirm the election of group I, claims 1-22, 25-42 and 44-45. Furthermore, Applicants have amended the pending claims to recite the elected species, namely a pharmaceutical formulation comprising azelastine and fluticasone.

New Claims

Applicants have added new claims 53-54 directed to specific combinations of azelastine and specific pharmaceutically acceptable esters of fluticasone, which are supported by paragraph 0045 of the published application. Further, Applicants have added new claims 55-56, which mirror existing claims 28 and 29, and are drawn to a nasal spray as disclosed by paragraph 0010 of the published application. The new claims are patentable for the reasons set forth below.

Claim Rejections – 35 U.S.C. § 112

Claims 6 and 18 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants have amended claim 6 to remove the term "about." Applicants have also amended claim 18 to remove the recitation of a narrower range of values. In consideration of the foregoing, Applicants respectfully request withdrawal of the rejections.

Claim Rejections – 35 U.S.C. § 102

Claims 1, 2, 4, 7, 9-10, 12-21, 30-31, and 44-45 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Cramer, European Patent No. 0780127 (hereinafter "*Cramer*"). Applicants note that claim 5 was not rejected as being anticipated by *Cramer*. Applicants have amended claim 1 to incorporate the limitations of now canceled claim 5 and respectfully submit that claims 1, 2, 4, 7, 9-10, 12-21, 30-31, and 44-45 are not anticipated by *Cramer*.

Claim Rejections – 35 U.S.C. § 103

Claims 1, 2, and 6 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Malmqvist-Granlund, et al., U.S. Patent No. 6,391,340 (hereinafter "*Malmqvist-Granlund*"). Applicants note that claim 5 was not rejected as being obvious in view of *Malmqvist-Granlund.* Applicants have amended claim 1 to incorporate the limitations of now canceled claim 5 and respectfully submit that claims 1, 2 and 6 are not obvious over *Malmqvist-Granlund.*

Claims 5 and 35-38 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over *Cramer*. Claims 22 and 26-27 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over *Cramer* in view of Modi, U.S. Patent No. 6,294,153 (hereinafter "*Modi*"). Claims 28-29 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over *Cramer* in view of Alfonso, et al., U.S. Patent No. 6,017,963 (hereinafter "*Alfonso*"). Accordingly, the pending claims stand or fall on the above-recited application of the primary reference, *Cramer*, alone or in combination with the secondary references, *Modi* or *Alfonso*, to independent claims 1, 26, 28, and 29. Applicants respectfully submit the pending claims are patentable because the broad genus disclosed in the primary reference does not render obvious the Applicants' claimed species directed to a pharmaceutical formulation comprising azelastine and fluticasone. Further, Applicants submit herewith objective evidence of nonobviousness in that the claimed species directed to a pharmaceutical formulation comprising azelastine and fluticasone displays unexpectedly beneficial properties, is commercially successful, and fills a long felt but unsolved need.

The Legal Standard for Obviousness

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

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

> [t]he factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:
>
> 1. Determining the scope and contents of the prior art.
> 2. Ascertaining the differences between the prior art and the claims at issue.
> 3. Resolving the level of ordinary skill in the pertinent art.

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

See Office Action at 10. In an attempt to satisfy the factual inquiries set forth in *Graham*, the Office Action addresses the "determining the scope and contents of the prior art" and "ascertaining the differences between the prior art and the claims at issue" portions of the *Graham* factual inquiries. However, the Office Action is silent with regards to the "resolving the level of ordinary skill in the pertinent art" and "considering objective evidence present in the application indicating obviousness or nonobviousness" portions of the *Graham* factual inquiries.

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

In ascertaining the difference in the prior art and claim 5, the Office Action acknowledges "Cramer does not exemplify a composition comprising azelastine and fluticasone." *See* Office Action at 12. As such, the Office Action retreats to a "rationale-based" obviousness rejection based on the conclusion that:

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

See Office Action at 12.

The Office Action then supports its "rationale-based" rejection by stating, "the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made **because the prior art is fairly suggestive of the claimed invention**." *See* Office Action at 13 (emphasis added). As noted previously, "establishing a *prima facie* case of obviousness" requires, "the clear articulation of the reason(s) why the claimed invention would have been obvious." *See* MPEP § 2142. The Office Action's conclusion does not support a *prima* *facie* case of obviousness because the Office Action does not clearly articulate why the claimed invention would be obvious.

The Office Action's reliance and discussion of *Cramer* does not articulate why the claimed pharmaceutical formulation comprising azelastine and fluticasone would be obvious in view of *Cramer's* general disclosure that mixtures of glucocorticoids and mixtures of antihstamines could be combined. The total number of **possible glucocorticoids specified in *Cramer* is six** (*beclomethasone, flunisolide, triamcinolone, fluticasone, mometasone and budesonide*) and the **total number of antihistamines is three** (*cetirizine, loratadine, azelastine*). Accordingly, there is a total of eighteen different combinations disclosed in *Cramer*. The present application claims just one of these combinations, and it is common ground that this particular combination (fluticasone and azelastine) is not explicitly mentioned in *Cramer*. The number of possible combinations rises exponentially when considering the breadth of the disclosed combinations of racemates, salts, and mixtures of the glucocorticoid and antihistamine agents.

As such, *Cramer*'s disclosure cannot be "fairly suggestive of the claimed invention," *see* Office Action at 13, because, as the MPEP states, the rationale for supporting an obviousness determination requires, "choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success." *See* MPEP § 2143; *see also KSR Int'l Co. v. Teleflex, Inc.*, 82 USPQ2d at 1397 (a combination of elements is obvious if "there are finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue."). Clearly, *Cramer*'s recitation of the possibility of innumerous combinations of compounds does not disclose a "finite number of identified, predictable solutions." *See id.*

Based on the foregoing, Applicants respectfully submit that the Office Action does not present a *prima facie* case of obviousness with regard to the instant claims.

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

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

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

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

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

These tests demonstrate that there is a clear unexpected advantage in product stability in formulating azelastine with fluticasone rather than with other steroids such as budesonide.

Improved product stability is extremely important in pharmaceutical compositions as is understood by those skilled in the art.

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

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

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

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

2. The combination of azelastine and fluticasone is commercially successful

Commercial success is a strong factor favoring nonobviousness. *See e.g., Akzo N.V.* at 1246. As noted in paragraph 3 of the declaration, a pharmaceutical formulation comprising azelastine and fluticasonse is commercially available where approved as DUONASE nasal spray. The doctor statements set forth in Exhibit B provide further evidence of the commercial success of DUONASE nasal spray. Furthermore, as noted in paragraph 5 of the declaration the present application claiming a pharmaceutical formulation comprising azelastine and fluticasonse is licensed to Meda Pharmaceuticals, which specializes in respiratory, allergy, and cough-cold products. Given its expertise and knowledge in the field of treatment, the willingness of Meda Pharmaceuticals to license the pending application is further evidence of the commercial success of the claimed pharmaceutical formulation comprising azelastine and fluticasone. Accordingly, the claimed pharmaceutical formulation comprising azelastine and fluticasone is nonobvious in view of its commercial success.

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

As set forth in *Graham*, the existence of a long-felt and unsolved need in the art is further evidence of nonobviousness. Applicants note that *Cramer* was published on June 25, 1997, which was over 10 years ago. Nonetheless, as noted in paragraph 5 of the declaration, inventor Geena Malhotra is unaware of another commercially available pharmaceutical formulation comprising an antihistamine and a steroid. Likewise, the doctor statement of Exhibit B4 notes that:

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

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

4. The secondary considerations require a finding of nonobviousness

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

CONCLUSION

Consideration of the foregoing amendments and remarks, reconsideration of the application, and withdrawal of the rejections are respectfully requested by Applicants. No new matter is introduced by way of the amendment. It is believed that each ground of rejection raised in the Office Action dated January 23, 2009 has been fully addressed. If any fee is due as a result of the filing of this paper, please appropriately charge such fee to Deposit Account Number 50-1515 of Conley Rose, P.C., Texas. If a petition for extension of time is necessary in order for this paper to be deemed timely filed, please consider this a petition therefore.

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

Respectfully submitted,
CONLEY ROSE, P.C.

Date: 7-23-09

Rodney B. Carroll
Reg. No. 39,624

ATTORNEY FOR APPLICANTS

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

EXHIBIT 1005(B)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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

DECLARATION UNDER 37 CFR § 1.132

I, Geena Malhotra, hereby declare and say that:

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

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

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

Table I of Exhibit A sets for the ingredient list for the five compositions. Table II of Exhibit A sets forth comparative stability data for the five compositions. The results in Table II show the impurity levels in the initial compositions, and after storage under certain conditions: for example "25/60 RH at 1 M" means the composition was stored for one month at a temperature of 25 degrees C and at a relative humidity of 60. The results in Table II show that the individual active materials (e.g., azelastine.HCl, budesonide, and fluticasone propionate) have good stability, in that the impurity levels are fairly constant in all the tests. The results in Table II also show that the combination of azelastine and budesonide are relatively unstable, with varying, and high amounts of impurities developing during the tests. Surprisingly, the results for azelastine and fluticasone show good stability throughout the tests, as the amount of impurity remains constant and at a low level.

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

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

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

6. The present application is licensed to Meda Pharmaceuticals.

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

Date: 3rd July 2009.

GMalhotra

Name: GEENA MALHOTRA

Exhibit A, Table I: Comparative Composition data of Azelastine with steroids

Ingredients	**Azelastin (%w/w)**	**Budesonide (%w/w)**	**Azelastine+Budesonide (%w/w)**	**Fluticasone (%w/w)**	**Aze+Flu (%w/w)**
Drugs	137 mcg	64 mcg	137+64 mcg	50 mcg	140+50 mcg
MCC+CMC (Avicel RC)	-	-	2.0	0.75	2.0
HPMC	0.10	-	-	-	-
Dispersible cellulose	-	1.25	-	-	-
Dextrose Anhy.	-	-	-	2.5	-
Anhy. Glucose	-	5.0	-	-	-
Glycerin	-	-	2.3		2.3
Polysorbate 80		0.016	0.005	0.0025	0.005
BKC 10% w/v solution	0.125	-	0.005	100 ml	0.10
Phenyl ethyl alcohol	-	-	-	0.125	0.25
Pot sorbate	-	0.12	-	-	-
Disodium EDTA	0.05	0.01	0.01		0.01
Sodium Chloride	0.68				
Citrate Monohydrate	0.048	-	-	-	-
Disodium Phosphate	0.322	-	-	-	-
Hydrochloric acid		q.s.			

Exhibit A, Table II: Comparative Stability data of Azelastine with steroid Compositions

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

Best Available Copy

Exhibit B1

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

Consultation:
Behind Margin Free Market
Near Kottayam East Police Station
Collectorate P.O., Kottayam - 686 002
Ph: 2564884, Mb: 9447288822

To Cipla Respiratory L

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

Kottayam
23/8/05

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

<u>Dr. C.M.MATHEW CHOORACKEN</u>

To Cipla Respiratory

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

Kottayam
23/8/05

Best Available Copy

Exhibit B2

Confidential

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

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

जय मेडिकल सेन्टर (वसावड़ा पेट्रोल पम्प के पा
घंटाघर, फ्रीगंज, उज्जैन ☎ 2514884
रविवार अवकाश समय सायं 6 से 8.30

विशेषज्ञ
• नाक एवं सायनस इन्डोस्कोपी (दूरबीन द्वारा आपरेशन) • माइक्रोलेरिन्जयल सर्जरी
• माइक्रोइयर सर्जरी (जर्मनी, फ्रांस एवं स्वीटजरलेण्ड से प्रशिक्षण प्राप्त) • नाक की प्लास्टिक सर्जरी (राईनोप्लास्टी)

18.8.200[illegible]

Regarding Duonase

Using this product for last so many days

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

- Acts on both phases (early as well as late phase of allergy i.e inhibit)
- prolongs the H1 receptor activity & few side effects.
- Acts on multiple symptoms

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

Tough to allergy safe to [illegible]

[signature]

DR.P.N.TEJANKAR

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

CLINIC

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

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

SUNDAY HOLIDAY

....**Specialist**.......................................

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

....

Regarding Duonase

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

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

- Antagonises the H1 receptor activity with few side effect.

- Acts on multiple symptoms.

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

Tough to allergy safe to Nose

Best Available Copy

Exhibit B3

Confidential

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

रजि. नं. ०७१८८२

कृष्णा जनरल हॉस्पिटल
गव्हाणे बिल्डींग, पी. सी. एम. टी. चौक, भोसरी,
पुणे ४११०३९. ☎ २७१२९५१६
वेळ : संध्या. ५.०० ते ८-०० वा.

(कान-नाक-घसा
धन्वंतरी कान, नाक, घसा हॉस्पि
ओझर रोड, नारायणगाव
ता. जुन्नर, जि. पुणे, ४१०
☎ ०२१३२ -(हॉस्पि.) २४४७६६, (नि.) २४२

रविवार बंद

Date. 27·8·05

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

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

[signature]

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

Reg.no.071882	E.N.T Specialist
Krishna General Hospital	Dhanvantari E.N.T.Hospital
Gavhane building, P.C.M.T Chowk,	Khodad Road, Narayangaon,
Bhosari,Pune 411039. ☎ 27129516	Taluka Junnar, Dist. Pune 410504
Time: eve. 5-00 to 8-00 SUNDAY CLOSED	☎02132-(Hosp.)244766 (R)243969

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

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

Best Available Copy

Exhibit B4

Confidential

Regn. No.: 25409

Dr. Manish Munjal

M.B.B.S., M.S. Diplomate of National Board (ENT); M.N.A.M.S.
D.H.A., D.N.D., D.N.A., D.T.M., DM.S.

EAR - NOSE - THROAT AND HEAD-NECK SURGEON

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

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

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

Sig.

An.
Pr.
Ro.
Lo.
Rin.
Web.
Cxp.
Adl.
Asso. Adl.
Under Treatment of:
Cross Consult:
Sm.

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

The present combination spray of a weak (non sedating component) Azelastine and fluticasone (steroidal component) is comp by itself in my patients of chronic simple rhinitis, following nasal + sinus polyposis surgery and those unwilling for surgery or unfit for surgery. There is a response noted within a week in a few patients but the maximum

N. Singh
Munjal

Confidential

number of patients respond very well after three weeks of therapy.

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

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

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

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

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

DR. MANISH MUNJAL

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

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

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

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

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

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

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

Best Available Copy

Exhibit B5

VATS E.N.T. CENTRE

(दिल्ली सरकार द्वारा पंजीकृत)

698/5, Yamuna Vihar Road, (Road No. 66), Maujpur, Delhi-110053

Ph. : 229111 : 22918[illegible] : 22911[illegible]

Dr. Suresh Vats

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

डॉ० सुरेश वत्स
एम.बी.बी.एस., एम.एस.(ई.एन.टी.)
कान, नाक व गला रोग विशेषज्ञ एवं सर्जन

समय : सुबह 10 से 1 तक शाम 6 से 9 तक

Reimbursable Yes/No. S. No. .... (रविवार अवकाश)

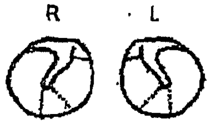
Name .... Age & Sex .... Resi. .... Date .... A[illegible]

रविवार को केवल Audiometry एवं Speech Therapy
रवि. बुध. शुक्र सुबह 10 से 1 व मंगल शाम 7 से 9 बजे
P.T. Audiogram/Hearing Assessment
[illegible] Audiogram
Hearing Aid Trial
Speech Assessment
Speech Therapy
Caloric Test
Impedance

Hb TLC, DLC, B.T., C.T.
ESR, Mx-Test
Blood Sugar R-F-Pp., Blood Urea
Urine R/E & M/c
Prothrombin time Platelets Count
HBsAg. HIV I & II
AEC IgE, Nasal smear for Eosinophils
VDRL, ASLO Titre
T3 T4 TSH
Sputum smear for AFB
Throat/Nasal/Ear/Swab C & S
Stool - ova & cyst
FNAC

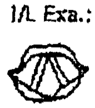
X-Ray Mastoids - Lat. Oblique(RL) Towns
X-Ray PNS - Waters
X-Ray Naso-Pharynx-soft Tissue (Lateral)
X-Ray Neck soft Tissue - Lateral
X-Ray cervical Spine - Lat. & A.P.
X-Ray - Styloid Process (B-Lateral)
X-Ray Occlusal view for of mouth
X-Ray - Submandibular region - Lat., Rt. - Lt.
X-Ray - Internal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

R L

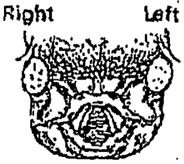


Rinne's
Weber's

I/L Exa.:



Right Left



Dutnase nasal spray is unique & distinct from available nasal spray due to its combined anti allergic & anti inflammatory properties. It is an excellent product, effective in my patients c Allergic Rhinitis with or without concomitant Bronchial

No Substitution [illegible]

Allergy: Worth Trying Say
to use in certain patients wh
oral antihistamine may be harm

17/8/08

Dr. SURESH VATS
M.S. (ENT)
Sr. CONSULTANT EAR, NOSE &
THROAT SURGEON
Reg. No. MCI-2108, DMC-1712
698/5, Road No 66, Manipur, Delhi-55

Dr. SURESH VATS

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

Best Available Copy

Exhibit B6

डॉ. बी. बी. माथुर
एम.डी.

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

Dr. B. B. Mathur
M.D.

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

Ref No.

Date 17/8/05

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

डॉ. बी. बी. माथुर
एसोसिएट प्रोफेसर
टी. बी. एवं चेस्ट विभाग
... मेडिकल कॉलेज
बीका... (राज.)

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

Dr. B.B. MATHUR

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

Exhibit C

Cipla Doc Your Window to the Wide World of Therapeutics

Cipla.com | Ciplaaids.org | Site map | Home

Essential Cipla Essential Tools Leisure Time

Cipla

Therapeutic Index

Nasal Preparations

Duonase Nasal Spray

Azelastine hydrochloride & Fluticasone propionate

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

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

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

Pharmacology
As Duonase is a combination of Azelastine and Fluticasone; the pharmacological properti both the molecules are given separately.
Pharmacology of Azelastine Hydrochloride
Azelastine hydrochloride, a phthalazinone derivative, exhibits histamine H 1 -receptor ant activity in isolated tissues, animal models, and humans. The major metabolite, desmethylazelastine, also possesses H 1 -receptor antagonist activity.

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

The major active metabolite, desmethylazelastine, was not measurable (below assay limi single-dose intranasal administration of azelastine hydrochloride. After intranasal dosing azelastine hydrochloride to steady-state, plasma concentrations of desmethylazelastine r from 20-50% of azelastine concentrations. When azelastine hydrochloride is administerec desmethylazelastine has an elimination half-life of 54 hours. Limited data indicate that the metabolite profile is similar when azelastine hydrochloride is administered via the intranas oral route.

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

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

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

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

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

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

Metabolism: The total blood clearance of fluticasone propionate is high (average, 1,09 mL/min), with renal clearance accounting for less than 0.02% of the total. The only circula metabolite detected in man is the 17(beta)-carboxylic acid derivative of fluticasone propio which is formed through the cytochrome P450 3A4 pathway. This inactive metabolite had affinity (approximately 1/2,000) than the parent drug for the glucocorticoid receptor of hum cytosol in vitro and negligible pharmacological activity in animal studies. Other metabolite detected in vitro using cultured human hepatoma cells have not been detected in man.

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

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

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

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

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

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

Contact Us

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

Therapeutic Index
Cipla
Cipla Omnicare

New Introductions
Internationally
Cipla
Protec

Essential Reading
Publications
Patient help
Treatment guidelines

Search:
Go
www
www.cipladoc.com

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

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

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

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

Shelf Life
2 years

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

Packaging Information
Duonase Nasal Spray
Sales pack contains 70 metered doses

Last Updated: M

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

EXHIBIT 1005(C)

UNITED STATES PATENT AND TRADEMARK OFFICE

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

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

30652 7590 04/28/2010

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

EXAMINER	
BROOKS, KRISTIE LATRICE	

ART UNIT	PAPER NUMBER
1616	

MAIL DATE	DELIVERY MODE
04/28/2010	PAPER

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

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

PTOL-90A (Rev. 04/07)

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

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

Period for Reply

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

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

Status

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

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

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

Disposition of Claims

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

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

5)☐ Claim(s) _____ is/are allowed.

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

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

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

Application Papers

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

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

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

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

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

Priority under 35 U.S.C. § 119

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

a)☐ All b)☐ Some * c)☐ None of:

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

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

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

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

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/23/09;8/7/09*.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application

6) ☐ Other: _____.

DETAILED ACTION

Status of Application

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

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

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

Claim Rejections - 35 USC § 103

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

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

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

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

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

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

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

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

Cramer teaches a nasal spray composition comprising about 0.001 to about 0.2% concentration of a glucocorticosteroid (i.e. beclomethasone, flunisolide, triamcinolone, fluticasone, mometasone, bedusonide and pharmaceutically acceptable salts), 0.01 to about 4% concentration of an antihistamine (i.e. azelastine or pharmaceutically acceptable salt thereof, and an intranasal carrier (see the abstract and page 2 lines 36-45). The composition may contain isotonic agents such as citric acid, boric acid, propylene glycol, etc., thickening agents such as xanthan gum, microcrystalline cellulose, carboxymethyl cellulose, hydroxypropyl cellulose, etc., humectants such as sorbitol, propylene glycol, polyethylene glycol, etc. and preservatives such as benzyl alcohol, phenylethyl alcohol, and quaternary ammoniums such as benzalkonium chloride (see page 4 lines 50-58 and page 5 lines 1-22). The composition may contain surfactants such as Polysorbate 80, Octoxynol, etc. (see page 5 lines 11-16). The pH of the composition is from about 4.5 to about 9 (see page 2 lines 57-58). The composition may be formulated into a nasal solution (for use as drops or a spray), a nasal suspension, ointment, or gel (see page 3 lines 43-47). Typically the dosage units may be prepared to deliver 0.5mcg to about 100mcg of the glucocorticoid and 5mcg to about 1000mcg of the antihistamine spray (see page 3 lines 58 and page 4 lines 1-2).

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

Component	Wgt %
triamcinolone acetonide	0.050
azelastine HCl	0.070
polysorbate 80	0.080
glycerin	2.000
hydroxypropyl methyl cellulose	1.000
sodium chloride	0.900
ethylenediamine tetraacetic acid	0.050
benzalkonium chloride	0.020
distilled water	q.s. to vol.

(see page 6, Example III).

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

Cramer does not exemplify a composition comprising azelastine and fluticasone.

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

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

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

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

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

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

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

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

Cramer teaches a nasal spray composition comprising about 0.001 to about 0.2% concentration of a glucocorticosteroid (i.e. beclomethasone, flunisolide, triamcinolone, fluticasone, mometasone, bedusonide and pharmaceutically acceptable salts), 0.01 to about 4% concentration of an antihistamine (i.e. azelastine or pharmaceutically acceptable salt thereof, and an intranasal carrier (see the abstract and page 2 lines 36-45). The composition may contain isotonic agents such as citric acid, boric acid, propylene glycol, etc., thickening agents such as xanthan gum, microcrystalline cellulose, carboxymethyl cellulose, hydroxypropyl cellulose, etc., humectants such as sorbitol, propylene glycol, polyethylene glycol, etc. and preservatives such as benzyl alcohol, phenylethyl alcohol, and quaternary ammoniums such as benzalkonium chloride (see page 4 lines 50-58 and page 5 lines 1-22). The composition may contain surfactants such as Polysorbate 80, Octoxynol, etc. (see page 5 lines 11-16). The pH of the composition is from about 4.5 to about 9 (see page 2 lines 57-58). The composition may be formulated into a nasal solution (for use as drops or a spray), a nasal suspension, ointment, or gel (see page 3 lines 43-47). Typically the dosage units may be prepared to deliver 0.5mcg to about 100mcg of the glucocorticoid and 5mcg to about 1000mcg of the antihistamine spray (see page 3 lines 58 and page 4 lines 1-2).

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

Component	Wgt %
triamcinolone acetonide	0.050
azelastine HCl	0.070
polysorbate 80	0.080
glycerin	2.000
hydroxypropyl methyl cellulose	1.000
sodium chloride	0.900
ethylenediamine tetraacetic acid	0.050
benzalkonium chloride	0.020
distilled water	q.s. to vol.

(see page 6, Example III).

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

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

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

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

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

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

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

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

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

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

Cramer teaches a nasal spray composition comprising about 0.001 to about 0.2% concentration of a glucocorticosteroid (i.e. beclomethasone, flunisolide, triamcinolone, fluticasone, mometasone, bedusonide and pharmaceutically acceptable salts), 0.01 to about 4% concentration of an antihistamine (i.e. azelastine or pharmaceutically acceptable salt thereof, and an intranasal carrier (see the abstract and page 2 lines 36-45). The composition may contain isotonic agents such as citric acid, boric acid, propylene glycol, etc., thickening agents such as xanthan gum, microcrystalline cellulose, carboxymethyl cellulose, hydroxypropyl cellulose, etc., humectants such as sorbitol, propylene glycol, polyethylene glycol, etc. and preservatives such as benzyl alcohol, phenylethyl alcohol, and quaternary ammoniums such as benzalkonium chloride (see page 4 lines 50-58 and page 5 lines 1-22). The pH of the composition is from about 4.5 to about 9 (see page 2 lines 57-58). The composition may be formulated into a nasal solution (for use as drops or a spray), a nasal suspension, ointment, or gel (see page 3 lines 43-47). Typically the dosage units may be prepared to deliver 0.5mcg to about 100mcg of the glucocorticoid and 5mcg to about 1000mcg of the antihistamine spray (see page 3 lines 58 and page 4 lines 1-2).

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

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

(see page 6, Example III).

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

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

Fassberg et al. teach aerosol formulations for nasal administration comprising 1,1,1,2 tetrafluoroethane and a medicament (see the abstract and column 3 lines 2-7). Examples of the medicaments include antihistamines and steroids (see column 5 lines 61-66). The particle size of the active compound ranges from 0.1-25µm (see column 6 lines 11-15). The formulation may optionally contain an excipient or surfactant (see the abstract).

Finding of prima facie obviousness Rational and Motivation

(MPEP 2142-2143)

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

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

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

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

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

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

Cramer teaches a nasal spray composition comprising about 0.001 to about 0.2% concentration of a glucocorticosteroid (i.e. beclomethasone, flunisolide, triamcinolone, fluticasone, mometasone, bedusonide and pharmaceutically acceptable salts), 0.01 to about 4% concentration of an antihistamine (i.e. azelastine or pharmaceutically acceptable salt thereof, and an intranasal carrier (see the abstract and page 2 lines 36-45). The composition may contain isotonic agents such as citric acid, boric acid, propylene glycol, etc., thickening agents such as xanthan gum, microcrystalline cellulose, carboxymethyl cellulose, hydroxypropyl cellulose, etc., humectants such as sorbitol, propylene glycol, polyethylene glycol, etc. and preservatives such as benzyl alcohol, phenylethyl alcohol, and quaternary ammoniums such as benzalkonium chloride (see page 4 lines 50-58 and page 5 lines 1-22). The pH of the composition is from about 4.5 to about 9 (see page 2 lines 57-58). The composition may be formulated into a nasal solution (for use as drops or a spray), a nasal suspension, ointment, or gel (see page 3 lines 43-47). Typically the dosage units may be prepared to deliver 0.5mcg to about 100mcg of the glucocorticoid and 5mcg to about 1000mcg of the antihistamine spray (see page 3 lines 58 and page 4 lines 1-2).

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

Component	Wgt %
triamcinolone acetonide	0.050
azelastine HCl	0.070
polysorbate 80	0.080
glycerin	2.000
hydroxypropyl methyl cellulose	1.000
sodium chloride	0.900
ethylenediamine tetraacetic acid	0.050
benzalkonium chloride	0.020
distilled water	q.s. to vol.

(see page 6, Example III).

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

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

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

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

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

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

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

Response to Arguments

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

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

This argument is not persuasive. Cramer specifically teaches a nasal spray comprising the combination of a glucocorticoid (i.e. fluticasone) and an antihistamine (i.e. azelastine). There are a limited number of glucocorticoids (six) and antihistamines (three) recited. It is well within the means for one of ordinary skill in the art to try the instant combination as there are a small number of actives to choose from. Furthermore, disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. *In re Susi*, 440 F.2d 442, 169 USPQ 423 (CCPA 1971).

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

1.132 Declaration

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

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

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

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

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

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

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

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

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

Conclusion

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

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

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

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

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

KB

/Mina Haghighatian/
Primary Examiner, Art Unit 1616

EXHIBIT 1005(D)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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

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

CERTIFICATE OF EFS-WEB FILING

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

Linda Kerrick

Linda Kerrick

AMENDMENTS AND RESPONSE TO
<u>FINAL OFFICE ACTION DATED APRIL 28, 2010</u>

Dear Sir:

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

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

Remarks/Arguments begin on page 9 of this paper.

LISTING OF CLAIMS

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

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

3. (Canceled)

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

5. (Canceled)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

23-25. (Canceled)

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

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

28-29. (Canceled)

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

31-34. (Canceled)

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

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

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

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

39-43. (Canceled)

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

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

46-52. (Canceled)

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

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

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

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

REMARKS/ARGUMENTS

Status of Claims

Claims 26, 27, and 30 have been amended.

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

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

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

Claim Amendments

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

Claim Rejections – 35 U.S.C. § 103

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

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

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

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

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

The Legal Standard for Obviousness

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

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

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

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

A. <u>*Cramer* does not fairly suggest the elected species</u>

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

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

See OA 01232009 at 12.

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

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

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

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

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

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

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

Exhibit A has been amended

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

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

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

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

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

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

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

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

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

Response to alleged deficiencies of 1.132 Declaration

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

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

Thirdly, the Office Action's asserts that "Applicant did not test against the closest prior art examples described in *Cramer* (see Example 3). Example 3 in *Cramer* discloses a composition comprising azelastine and triamcinolone." *See* Office Action at 16. However, Applicants note that *Cramer* specifically treats fluticasone and budesonide as alternatives. *See Cramer*, claim 3. In view of the teachings of the Office Action's cited reference, *Cramer*, the ordinarily skilled artisan would consider the appropriate comparatives to be that of azelastine and fluticasone to azelastine and budesonide. Applicants respectfully submit that such comparatives which are made in the aforementioned declaration are both appropriate and convincing as to the beneficial features associated with the azelastine/fluticasone composition.

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

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

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

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

The Office Action also makes statements that addition of a preservative prevents the decomposition of a substance or inhibits the multiplication of organisms which also causes decomposition. *See* Office Action at 15. The Office Action then refers the Applicants to two general references regarding the use of preservatives and cites a passage in *Cramer* regarding preservatives. However, the Office Action fails to establish that the microorganisms whose growth are inhibited by phenyl ethyl alcohol inherently impact the stability of azelastine and/or fluticasone but rather that such organisms *may* impact the stability of these materials. The fact that a certain result or characteristic **may** occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art) (emphasis added); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is **necessarily present** in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (emphasis added). As the Office Action has failed to establish that microorganisms inhibited by the presence of phenyl ethyl alcohol *necessarily* affect the stability of azelastine and/or fluticasone, Applicants respectfully assert that the submitted experimental showings would lead one of ordinary skill in the art to conclude the azelastine and fluticasone composition displays an unexpectedly beneficial stability when compared to the azelastine and budesonide composition. *See Inventor Declaration at 6.*

2. The combination of azelastine and fluticasone is commercially successful

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

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

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

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

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

4. The secondary considerations require a finding of nonobviousness

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

CONCLUSION

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

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

Respectfully submitted,
CONLEY ROSE, P.C.

Date: 9-24-10

Rodney B. Carroll
Reg. No. 39,624

ATTORNEY FOR APPLICANTS

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

EXHIBIT 1005(E)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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

DECLARATION UNDER 37 CFR § 1.132

I, Geena Malhotra, hereby declare and say that:

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

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

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

Table I of Exhibit A sets for the ingredient list for the five compositions. Table II of Exhibit A sets forth comparative stability data for the five compositions. The results in Table II show the impurity levels in the initial compositions, and after storage under certain conditions: for example "25/60 RH at 1 M" means the composition was stored for one month at a temperature of 25 degrees C and at a relative humidity of 60. The results in Table II show that the individual active materials (e.g., azelastine.HCl, budesonide, and fluticasone propionate) have good stability, in that the impurity levels are fairly constant in all the tests. The results in Table II also show that the combination of azelastine and budesonide are relatively unstable, with varying, and high amounts of impurities developing during the tests. Surprisingly, the results for azelastine and fluticasone show good stability throughout the tests, as the amount of impurity remains constant and at a low level.

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

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

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

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

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

8. The present application is licensed to Meda Pharmaceuticals.

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

Date: September 23, 2010

GMalhotra

Geena Malhotra

EXHIBIT A

Comparative Composition data of Azelastine with steroids

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

Comparative Stability data of Azelastine with steroid Compositions

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

Exhibit B1

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

Consultation:
Behind Margin Free Market
Near Kottayam East Police Station
Collectorate P.O., Kottayam - 686 002
Ph: 2564884, Mb: 9447288822

To Cipla Respiratory L

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

Kottayam
23/8/05

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

Dr. C.M.MATHEW CHOORACKEN

To Cipla Respiratory

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

Kottayam
23/8/05

Exhibit B2

Confidential

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

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

जय मेडिकल सेन्टर (धरावड़ा पेट्रोल पम्प के पा
चंडाघर, फ्रीगंज, उज्जैन ☎ 2514884
समय सायं 6 से 8.30

रविवार अवकाश

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

18.8.[illegible]

<u>Regarding Duonase</u>

Using this product for last so many days.

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

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

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

Tough to allergy Safe to [illegible]

[illegible]

DR.P.N.TEJANKAR

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

CLINIC

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

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

SUNDAY HOLIDAY

Specialist

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

Regarding Duonase

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

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

- Antagonises the H1 receptor activity with few side effect.

- Acts on multiple symptoms.

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

Tough to allergy safe to Nose

Exhibit B3

Confidential

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

रजि. नं. ०७१८८२
कृष्णा जनरल हॉस्पिटल
गव्हाणे बिल्डींग, पी. सी. एम टी. चौक, भोसरी,
पुणे ४११०३९. ☎ २७१२९५१६
वेळ : संध्या. ५ .०० ते ८-०० वा.

रविवार बंद

(सोम---गुरू-घसा
धन्वंतरी कान, नाक, घसा हॉस्पि
ओतूर रोड, नारायणगाव
ता. जुन्नर, जि. पुणे, ४१०
☎ ०२१३२ –(हॉस्पि.) २४४७६६, नि. २४३

Date. 27·8·05

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

[signature]

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

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

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

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

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

Exhibit B4

Confidential

No: 25469

Dr. Manish Munjal

M.B.B.S., M.S. Diplomate of National Board (ENT), M.N.A.M.S.
D.H.A., D.N.D., D.N.A., D.T.M., DM.S.

EAR - NOSE - THROAT AND HEAD-NECK SURGEON

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

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

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

To

Ag.

Ar.

Pr.

Asso. Aid.

Ro

Lo

Under Treatment of:

Rin.

Cross Consult:

Wch.

Opp.

Sum.

Jll.

I have been using nasal sprays from the year 1993, ever since I joined my present institution. I have used beclomethasone, budesonide, Azelastine, fluticasone, mometasone, with oral antihistamines down the line till date.

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

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

N. Munjal

Munjal

number of patients respond very well after three weeks of therapy.

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

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

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

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

Hoping the future is bright for this combination and no one digs up some contraindication or sideeffect of

DR. MANISH MUNJAL

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

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

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

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

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

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

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

Exhibit B5

VATS E.N.T. CENTRE

(दिल्ली सरकार द्वारा पंजीकृत)

698/5, Yamuna Vihar Road, (Road No. 66), Maujpur, Delhi-110053

Ph. : 229111 / 22916[illegible] / 22911[illegible]

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

डॉ० सुरेश वत्स
एम.बी.बी.एस., एम.एस.(ई.एन.टी.)
कान, नाक व गला रोग विशेषज्ञ एवं सर्जन
समय : सुबह 10 से 1 तक शाम 6 से 8 तक
Reimbursable Yes/No. S. No. .... (रविवार अवकाश)

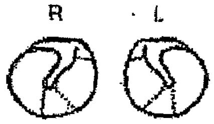
Name .... Age & Sex .... Regd. .... Date .... AM

परिक्षण की सुविधा Audiometory एवं Speech Therapy
रवि. बुध. शुक्र सुबह 10 से 1 व मंगल शाम 7 से 8 बजे
P.T. Audiogram/Hearing Assessment
Aided Audiogram
Hearing Aid Trial
Speech Assessment
Speech Therapy
Caloric Test
Impedance

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

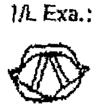
X-Ray Mastoids - Lat. Oblique(Bil) Towns
X-Ray PNS - Waters
X-Ray Naso-Pharynx soft Tissue (Lateral)
X-Ray Neck soft Tissue - Lateral
X-Ray cervical Spine - Lat. & A.P.
X-Ray - Styloid Process (Bi-Lateral)
X-Ray Occlusal view for of mouth
X-Ray - Submandibular region - Lat. Rt. - Lt
X-Ray - Internal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

R L

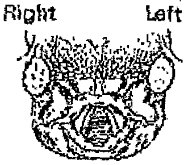


Rinne's
Weber's

I/L Exa.:



Right Left



Duenase nasal spray
is unique & distinct fr
other available nasal spr
due to its combined anti
allergic & antiinflammatory
properties. It is an excel
product, effective in the
patients c Allergic
Rhinitis with or w/o
concomitant Bronchia

Allergy: Worth trying spray
to use in certain patients wh
oral antihistamine may be harmy

17/8/08

Dr. SUMESH VATS
M.S. (ENT)
Sr. CONSULTANT EAR, NOSE &
THROAT SURGEON
Reg. No. MCI-2108, DMC-1712
698/5, Road No 06, Mangpur, Delhi-53

Dr. SURESH VATS

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

Exhibit B6

डॉ. बी. बी. माथुर
एम.डी.

वरिष्ठ विशेषज्ञ एवं एसोसियट प्रोफेसर
चेस्ट एवं टी.बी. विभाग
सरदार पटेल मेडिकल कॉलेज, बीकानेर
RMC No. 7458

Dr. B. B. Mathur
M.D.

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

Ref No.

Date 17/8/05

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

[signature]

डॉ. बी. बी. माथुर
एसोसियट प्रोफेसर
टी. बी. एवं चेस्ट विभाग
... मेडिकल कॉलेज
... (राज.)

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

Dr. B.B. MATHUR

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

Exhibit C

Cipla

Therapeutic Index

Nasal Preparations

Duonase Nasal Spray

Azelastine hydrochloride & Fluticasone propionate

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

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

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

Pharmacology
As Duonase is a combination of Azelastine and Fluticasone; the pharmacological properti both the molecules are given separately.
Pharmacology of Azelastine Hydrochloride
Azelastine hydrochloride, a phthalazinone derivative, exhibits histamine H 1 -receptor ant activity in isolated tissues, animal models, and humans. The major metabolite, desmethylazelastine, also possesses H 1 -receptor antagonist activity.

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

The major active metabolite, desmethylazelastine, was not measurable (below assay limi single-dose intranasal administration of azelastine hydrochloride. After intranasal dosing azelastine hydrochloride to steady-state, plasma concentrations of desmethylazelastine r from 20-50% of azelastine concentrations. When azelastine hydrochloride is administerec desmethylazelastine has an elimination half-life of 54 hours. Limited data indicate that the metabolite profile is similar when azelastine hydrochloride is administered via the intranas oral route.

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

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

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

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

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

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

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

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

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

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

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

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

Warnings and Precautions

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

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

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

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

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

Shelf Life
2 years

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

Packaging Information
Duonase Nasal Spray
Sales pack contains 70 metered doses

Last Updated: M

Contact Us

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

Therapeutic Index
- Cipla
- Cipla Omnicare

New Introductions
- Internationally
- Cipla
- Protec

Essential Reading
Publications
Patient help
Treatment guidelines

Search:
Go
www
www.cipladoc.com

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

Exhibit D

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

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

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

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

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

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

EXHIBIT 1005(F)

UNITED STATES PATENT AND TRADEMARK OFFICE

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

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

30652 7590 02/16/2011
CONLEY ROSE, P.C.
5601 GRANITE PARKWAY, SUITE 750
PLANO, TX 75024

EXAMINER	
NIELSEN, THOR B	
ART UNIT	**PAPER NUMBER**
1616	
MAIL DATE	**DELIVERY MODE**
02/16/2011	PAPER

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

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

PTOL-90A (Rev. 04/07)

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

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

Period for Reply

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

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

Status

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

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

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

Disposition of Claims

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

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

5)☐ Claim(s) _____ is/are allowed.

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

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

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

Application Papers

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

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

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

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

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

Priority under 35 U.S.C. § 119

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

a)☐ All b)☐ Some * c)☐ None of:

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

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

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

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

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/24/2010; 10/19/2010* .

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application

6) ☐ Other: _____.

DETAILED ACTION

Status of Examination

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

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

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

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

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

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

Status of Claims

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

Anticipation rejection, reinstated in part and new in part

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

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

Claim Rejections - 35 USC § 102

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

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

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

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

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

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

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

Claim Rejections - 35 USC § 103

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

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

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

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

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

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

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

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

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

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

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

Finding of *prima facie* Obviousness Rationale and Motivation

(MPEP 2142-2143)

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

Response to Remarks and Arguments

Applicant's arguments with regard to obviousness of claims 1-2, 9-10, 12-21, 30, 45, and 55-56 is mooted by the new or reinstated anticipation rejection. Thus, Applicant's arguments will be considered in view of the remaining claims: 4, 6-8, 11, 22, 26-27, 35-38, 44, 53, and 54.

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

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

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

Applicant characterizes the rejection as an obvious-to-try rejection. Amendment of September 24, 2010, *at* page 11. Applicant, quoting *In re Kubin,* further asserts that an obvious-to-try rejection requires an indication of which parameters were critical or which of many possible choices is likely to be successful. 90 USPQ2d 1417, 1423 (Fed. Cir. 2009) ('[W]here a defendant merely throws metaphorical darts at a board filled with combinatorial prior art possibilities, court should not succumb to hindsight claims of obviousness.")

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

B. Argument for secondary considerations

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

Both the current and previous Declarations had the statement in which the Declarant "declare[d] that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine, imprisonment, or both . . . and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon." E.g., Declaration dated September 23, 2010, page 3.

Second Declaration under 37 CFR 1.132

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

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

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

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

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

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

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

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

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

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

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

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

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

Applicant further asserts that the Declaration's Exhibits B1 and B3 demonstrate that a formulation of Azelastine and Fluticasone has unexpected efficacy when administered to patients, specifically that the product is very effective when compared [to] available other nasal sprays. *At* page 14, quoting an Exhibit. Applicant also notes that another physician wrote that the combination formulation "is very, very effective in all types of allergic rhinitis" and a "single drug was not effective as compared with the combination of both."

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

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

The applicant is arguing a feature not claimed.

Response to alleged deficiencies of 1.132 Declaration

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

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

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

Third, in response to the examiner's comment that the Applicant did not test against the closest prior art examples disclosed in Cramer, Applicant noted that Cramer treated Fluticasone and Budesonide as alternatives. Thus, one of skill in the art would consider the appropriate comparative to be the one tested.

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

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

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

This argument is mooted by the current rejection.

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

This argument is also mooted by the current rejection.

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

The argument is moot.

2. The combination of Azelastine and Fluticasone is commercially successful

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

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

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

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

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

Conclusion

All pending claims are rejected.

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

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

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

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

Thor Nielsen
Patent Examiner

/Johann R. Richter/

Supervisory Patent Examiner, Art Unit 1616

EXHIBIT 1005(G)

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	§	

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.

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. <u>In an embodiment, the formulation contains from about 50 micrograms to about 1 milligram of surfactant per ml of the formulation.</u>

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 <u>jet</u> (a stream of liquid forcefully shooting forth from the orifice) and <u>not a spray</u> (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 <u>undesirable hyperosmotic</u> (i.e., 554 mOsm/kg), <u>hypertonic character</u> 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, **<u>but only for what is disclosed in it</u>**." *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.

<u>3. The present invention has been commercially successful, leading to copying by others</u>

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
Reg. No. 39,624

ATTORNEY FOR APPLICANTS

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

EXHIBIT 1005(H)

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

	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

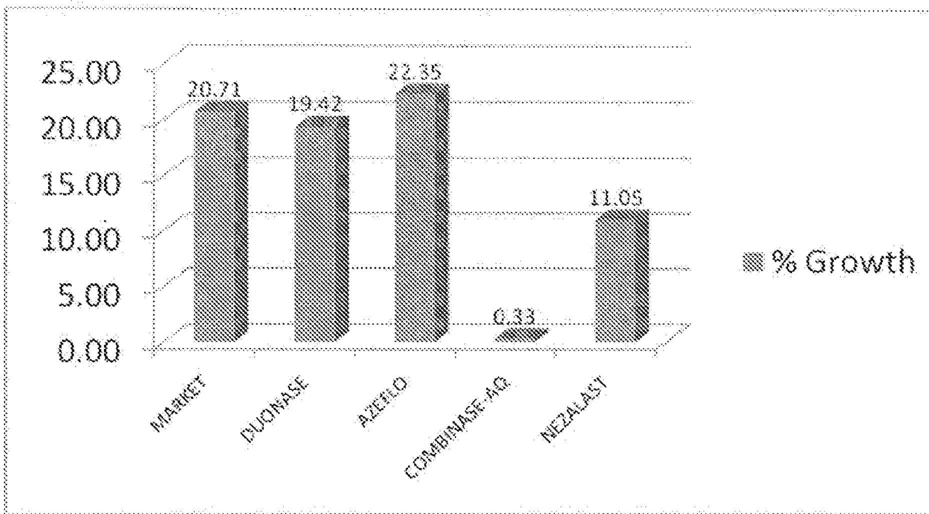
PRODUCT DESC		LAUNCH	MAT ~ 03/2005	MAT ~ 03/2006	MAT ~ 03/2007	MAT ~ 03/2008	MAT ~ 03/2009	MAT ~ 03/2010	MAT ~ 03/2011
	COMPANY		UNITS	UNITS	UNITS	UNITS	UNITS	UNITS	UNITS
SELECTED TOTAL			167,826	254,972	348,373	545,163	633,464	771,417	918,920
DUONASE	CIPLA	200404	167,826	240,271	263,680	350,072	398,499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

1315614/4D158700

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

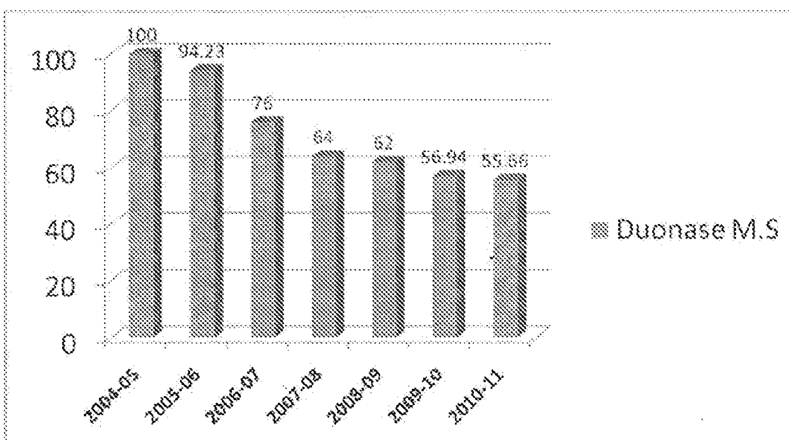
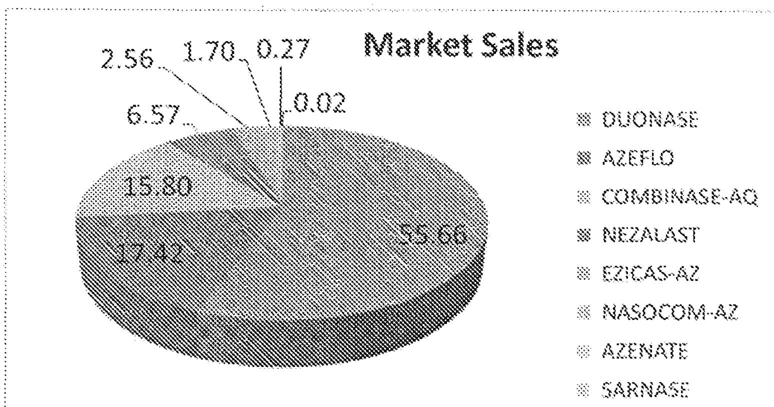


Fig. 3



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

EXHIBIT 1005(I)

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

Gmalhotra

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

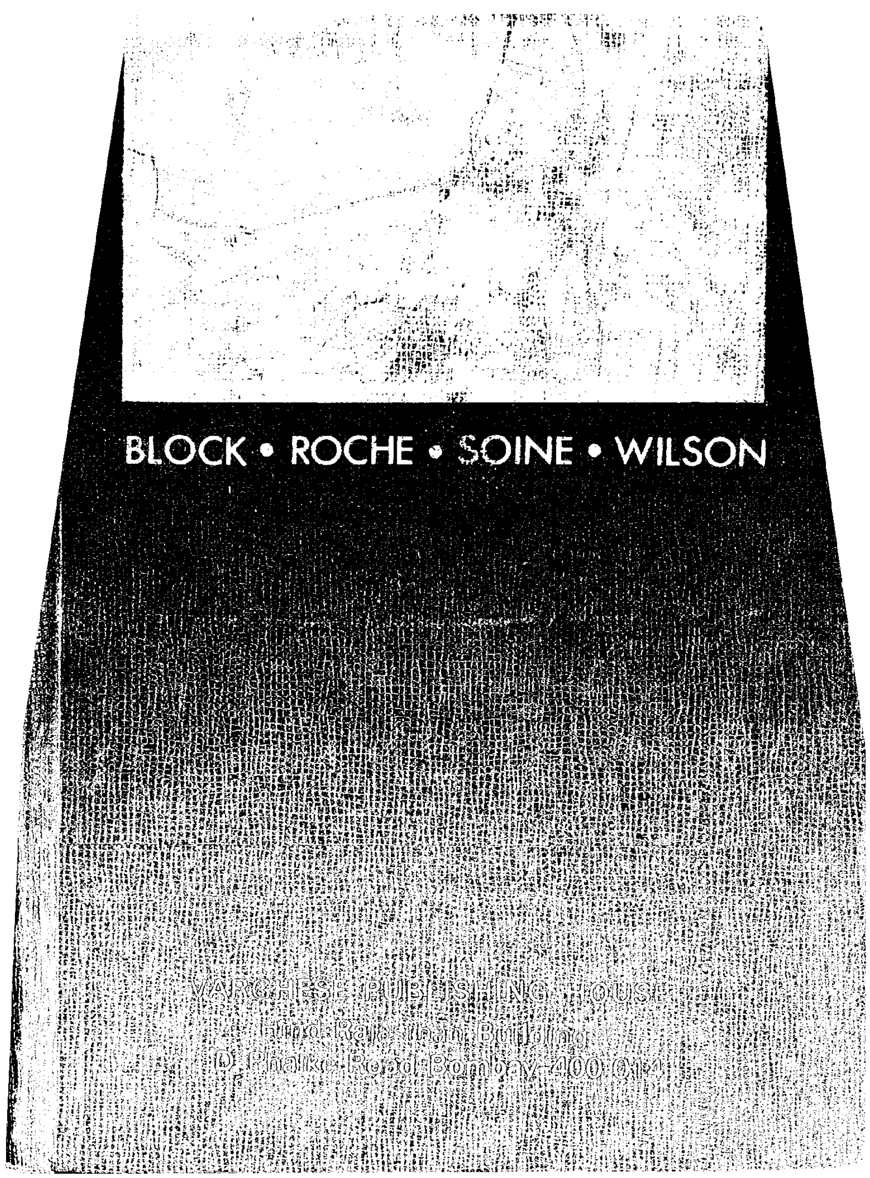
1. Cyclosporine Formulations (AU706995).
2. Benzimidazole pharmaceutical composition and process of preparation (WO9852564); Granted in GB (GB2343117).
3. Topical sprays (WO00/45795).
4. A pharmaceutical composition containing Bisphosphonic acid(s) or salt(s) thereof and a process for preparing thereof (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).

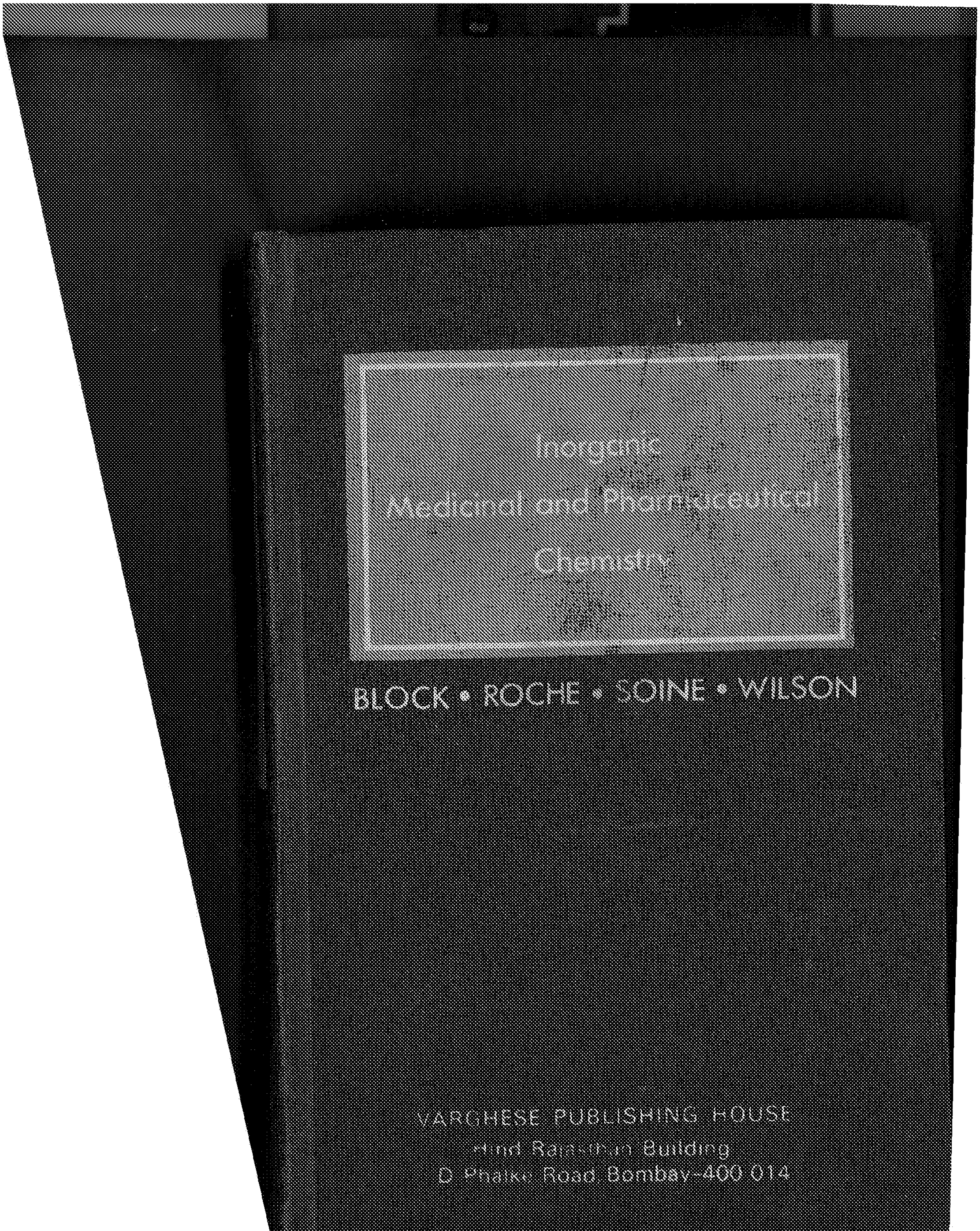
12. Pharmaceutical formulation including a suspension of Cefadroxil (ZA2000/7740).
13. An improved device for administering orally or nasally the powdered or volatile composition by inhalation (IN188288); Granted in South Africa & Sri Lanka.
14. Bilayered tablet containing Lamivudine, Stavudine & Nevirapine (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).

Exhibit B


BLOCK • ROCHE • SOINE • WILSON
VARGHESE PUBLISHING HOUSE
Hind Rajasthan Building
D. Phalke Road Bombay 400 014


Inorganic
Medicinal and Pharmaceutical
Chemistry
BLOCK • ROCHE • SOINE • WILSON
VARGHESE PUBLISHING HOUSE
Hind Rajasthan Building
D Phalke Road, Bombay-400 014

Inorganic Medicinal and Pharmaceutical Chemistry

JOHN H. BLOCK, Ph.D.
Associate Professor of Pharmaceutical Chemistry
Oregon State University
School of Pharmacy
Corvallis, Oregon

EDWARD B. ROCHE, Ph.D.
Associate Professor of Medicinal Chemistry
University of Nebraska Medical Center
College of Pharmacy
Omaha, Nebraska

TAITO O. SOINE, Ph.D.
Professor of Medicinal Chemistry and Chairman, Department of Medicinal Chemistry
University of Minnesota
Minneapolis, Minnesota

CHARLES O. WILSON, Ph.D.
Professor Emeritus of Pharmaceutical Chemistry
Oregon State University
School of Pharmacy
Corvallis, Oregon

INDIAN EDITION

VARGHESE PUBLISHING HOUSE
Hind Rajasthan Building
Dadar Bombay 400 014

1986

ion Data

emistry.

cal.
Pharmaceutical. QV744 I58 1974]

with Lea & Febiger

in Building Dadar

mbay 400 031.

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 Technology

Exhibit C

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

Development of Nasal Delivery Systems: A Review

NASAL DELIVERY

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.

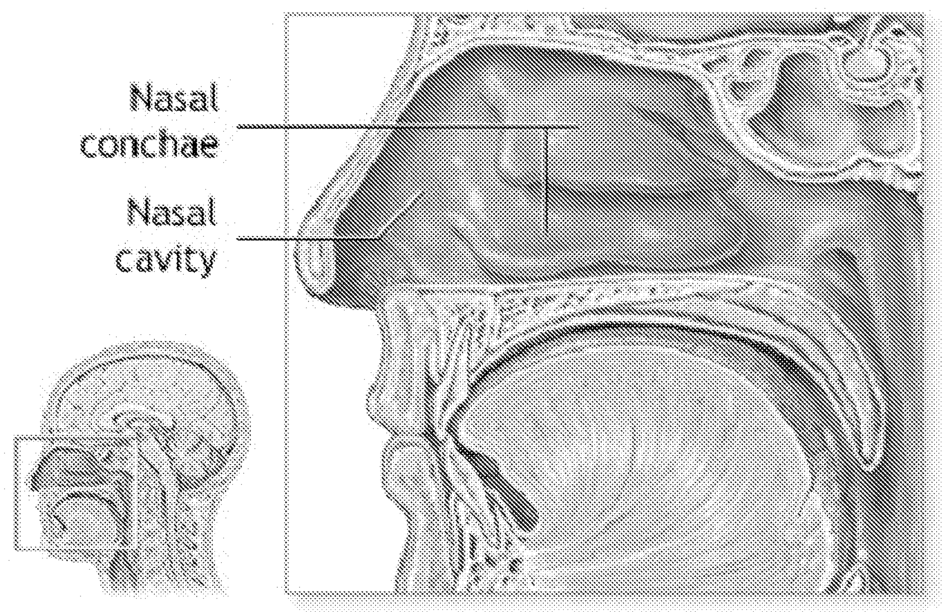
ANATOMY & PHYSIOLOGY OF THE NOSE

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.

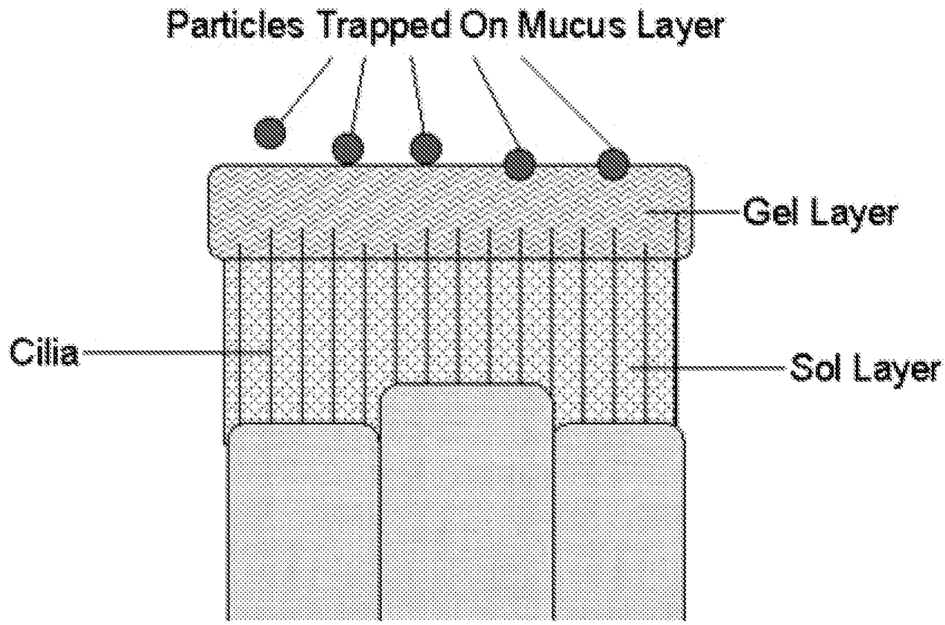
Harris[3] compared the deposition and removal of metered dose sprays with nasal drops. Nasal sprays were deposited anteriorly, after which small portions were cleared slowly into nasal pharynx by mucociliary clearance. In contrast, drops were deposited mostly posteriorly and were removed rapidly in large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

FIGURE 2

Mucociliary Clearance of the Nose



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

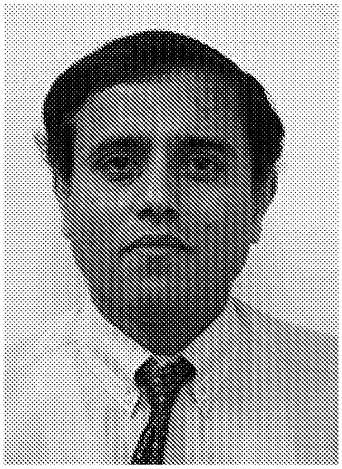
In order to formulate a nasal formulation with desirable performance and commercial attributes, the drug properties, delivery system and nasal physiology should all be considered and understood from the early stages of a product development. It is advisable to focus on maximizing the residence time and 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.

REFERENCES

1. Smith EL, Hill RL, Borman A. Activity of insulin degraded by aminopeptidase. Biophys Acta. 1958;29:207.
2. Dominique D, Gilles P. Nasal administration: a tool for tomorrow's systemic administration of drugs. Drug Develop Indust Pharmacy.1993;19 (1&2): 101-122.
3. Harris AS. Review: clinical opportunities provided by the nasal administration of peptides. J Drug Target. 1993;I:101-116.
4. Hussain AA. Intranasal drug delivery: Advanced Drug Delivery Rev. 1998;29:39-49.
5. Harris AS, Nilsson IM, Wagner ZG, Alkner U. Intranasal administration of peptides: nasal deposition biological response and absorption of desmopressin. J Pharm Sci. 1986 ;75:1085-1088.
6. Hussain A, Hirai S, Bawarshi R. Nasal absorption of the natural contraceptive steroid in rats—progesterone absorption. Letter in: J Pharm Sci. 1981;70:466-467.
7. Huang C, Kimura R, Nassar A, Hussain A. Mechanism of nasal drug absorption of drug II: absorption of L-tyrosine and the effect of structural modification on its absorption. J Pharm Sci. 1985;74:1298-1301.
8. Behl CR, Pimplaskar HK, Sileno J, deMeireles J, Romeo VD. Effects of physicochemical properties and other factors on systemic nasal drug delivery. Advanced Drug Delivery Rev. 1998;29:89-116.
9. Bjork E, Edman P. Characterization of degradable starch microspheres as a nasal delivery system for drugs. Int J Pharm. 1990;62:187-192.
10. Edman P, Bjork E, Ryden I. Microspheres as nasal delivery system for peptide drugs. J Controlled Release. 1992;21:165-172.
11. Hirai S, Yashika T, Matsuzawa T, Mima H. Absorption of drugs from the nasal mucosa of rat. Int J Pharm. 1981;7: 317-325.
12. Thompson R. Lysozyme and its relation to antibacterial properties of various tissues and secretions. Arch Pathol. 1940;30:1096.
13. Pennington AK, Ratcliffe JH, Wilson CG, Hardy JG. The influence of solution viscosity on nasal spray deposition and clearance. Int J Pharm. 1988;43:221-224.

14. Suzuki Y, Makino Y. Mucosal drug delivery using cellulose derivatives as a functional polymer. J Controlled Release. 1999;62:101-107.
15. Van de Donk HJM, Muller Plantema IP, Zuidema J, Merkus FWHM. The effects of preservatives on the ciliary beat frequency of chicken embryo tracheas. Rhinology. 1980;18:119-130.

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.

EXHIBIT 1005(J)

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

Dr. med. Joachim Maus

Ludwigstraße 30
D-63165 Mühlheim am Main
Tel. ++49-(0)6108-81448
Cell phone ++49-(0)172-66 10 579
Fax ++49-(0)6108-790115
Email: joachimg_maus@yahoo.de

CURRICULUM VITAE

Name:	Maus
Prename:	Joachim
Date of Birth:	January 26, 1967
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)

1

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

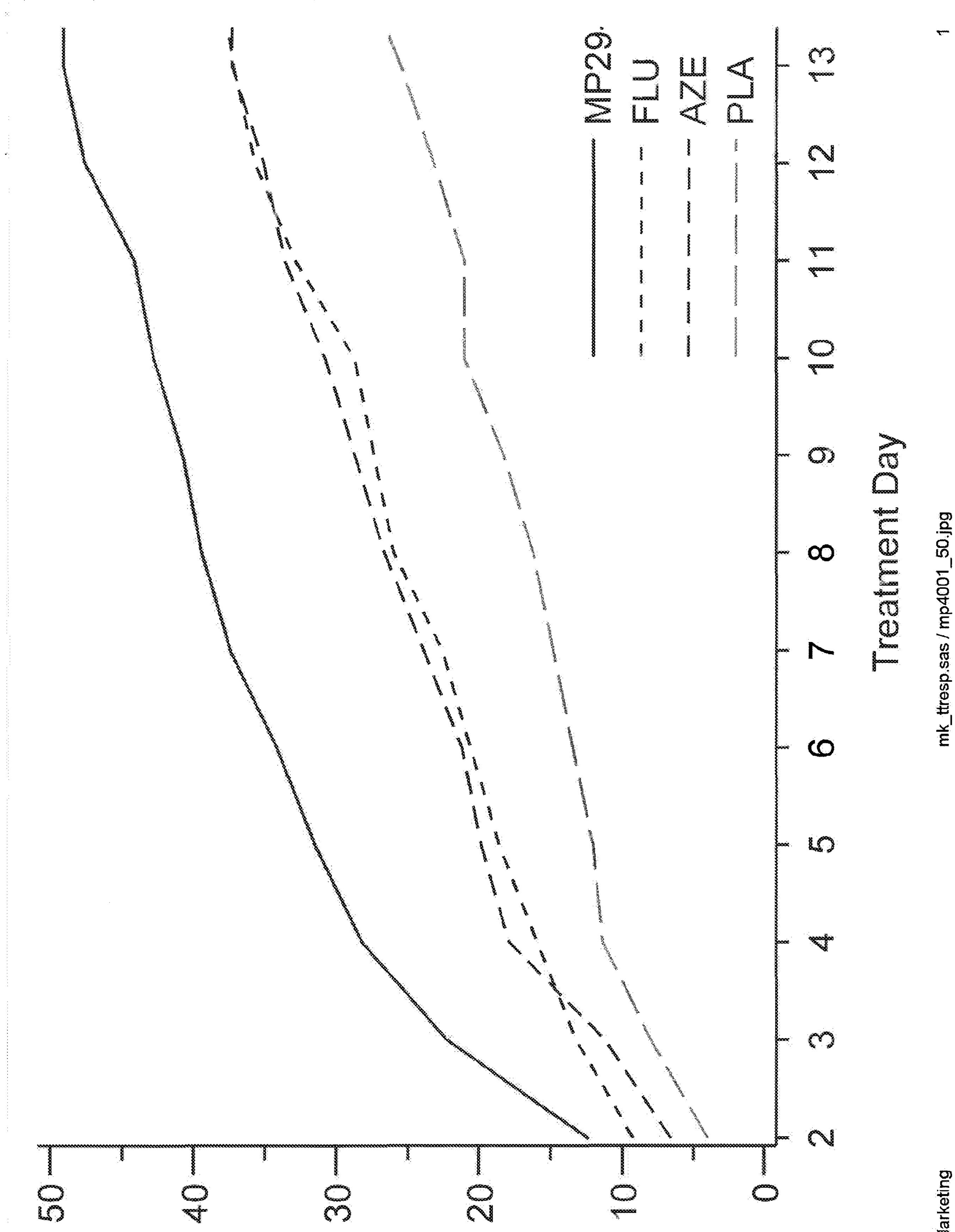

MP29.
FLU
AZE
PLA
Treatment Day
2
3
4
5
6
7
8
9
10
11
12
13
0
10
20
30
40
50
mk_ttresp.sas / mp4001_50.jpg
larketing
1

Exhibit C

WISCONSIN | Information Retrieval For Business and Industry

TECH SEARCH

WTS Number: 678749

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 Washington, DC 20005
Company Phone:	202-371-2600
Requester Phone:	202-772-8789
Fax:	202-371-2540
Requester Email:	Tjones@skgf.com
Send-To Email:	Tjones@skgf.com
Reference:	2286.0030002

RUSH

Delivery: **Email**

Instructions:

1}Juniper et al., J. Allergy Clin. Immunol. 83(3):627-633 (1989);

Med
φ
75796

0091-6749

An outreach service of the Kurt F. Wendt Library, University of Wisconsin - Madison
Email: wts@engr.wisc.edu | Web: http://www.wisc.edu/techsearch | Phone: (608) 262-5917

Requester assumes responsibility for copyright compliance.

Refer Off Campus

HDL

THE JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY

VOL. 83, NO. 3
MARCH 1989

Table of contents listed on pages 3A, 5A, 7A, and 8A

OFFICIAL PUBLICATION OF

AMERICAN ACADEMY OF ALLERGY AND IMMUNOLOGY

Forty-sixth Annual Meeting

March 23-28, 1990
Baltimore Convention Center
Baltimore, Md.

Published monthly by The C.V. Mosby Company
ISSN 0091-6749

THE JOURNAL OF

ALLERGY

AND

CLINICAL IMMUNOLOGY

VOLUME 83 Mosby NUMBER 3

CONTENTS

March 1989

Original articles

Contents continued on page 5A

Vol. 83, No. 3, March 1989. THE JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY (ISSN 0091-6749) is published monthly by The C.V. Mosby Company, 11830 Westline Industrial Drive, St. Louis, MO 63146-3318; phone (314) 872-8370, ext. 351. Second class postage paid at St. Louis, Mo., and additional mailing offices. POSTMASTER: Send address changes to THE JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY, 11830 Westline Industrial Drive, St. Louis, MO 63146-3318.

1989 Annual subscription rates	*U.S.A.*	*International (surface mail) All regions*	*International (airmail)**				
			Canada	*Mexico*	*Region 1*	*Region 2*	*Region 3*
Institutional†	$106.00	$127.00	$158.00	$164.25	$176.50	$218.25	$260.00
Individual‡	$ 50.00	$ 71.00	$102.00	$108.25	$120.50	$162.25	$204.00
Student, resident‡	$ 32.00	$ 53.00	$ 84.00	$ 90.25	$102.50	$144.25	$186.00

Single copies are $8.00. Remittances should be made by check, draft, or post office or express money order, in U.S. funds, drawn through a US bank, payable to this JOURNAL. Claims for missing issues will be serviced only within 6 months of cover date. Single copy price will be charged on missing issues older than 6 months from cover date.

**Airmail breakdown—Domestic:* First-class and Priority rates for the US and possessions are available upon request. *Canada:* All provinces of Canada. *Mexico:* All localities within Mexico. *Region 1:* Colombia, Venezuela, Central America, Caribbean Islands, Bahamas, Bermuda, and St. Pierre and Miquelon (also, from American Samoa to Western Samoa, and from Guam to the Philippines). *Region 2:* South America (except Colombia and Venezuela), Europe (except Estonia, Latvia, Lithuania and USSR), and North Africa (Morocco, Algeria, Tunisia, Libya, and Egypt). *Region 3:* Estonia, Latvia, Lithunia, USSR, Asia, Australia, New Zealand, Pacific Ocean Islands, Africa (other than North Africa), Indian Ocean Islands, and the Middle East.

†Institutional (multiple-reader) subscriptions are available to public and private libraries, schools, hospitals, and clinics; city, county, state, provincial, and national government bureaus and departments; and all commercial and private institutions and organizations.

‡Individual subscriptions and all student-rate subscriptions must be in the names of, billed to, and paid by individuals. All student-rate requests must indicate training status and name of institution.

Subscriptions may begin at any time.

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.

From the Departments of Medicine and Paediatrics, St. Joseph's Hospital and McMaster University, Hamilton, Ontario, Canada.
Supported by Glaxo Canada, Inc., Toronto, Ontario, Canada.
Received for publication April 15, 1988.
Accepted for publication July 15, 1988.
Reprint requests: E. F. Juniper, MSc, Department of Clinical Epidemiology and Biostatistics, McMaster University Medical Center, 1206 Main St., West, Hamilton, Ontario, Canada L8N 3Z5.

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

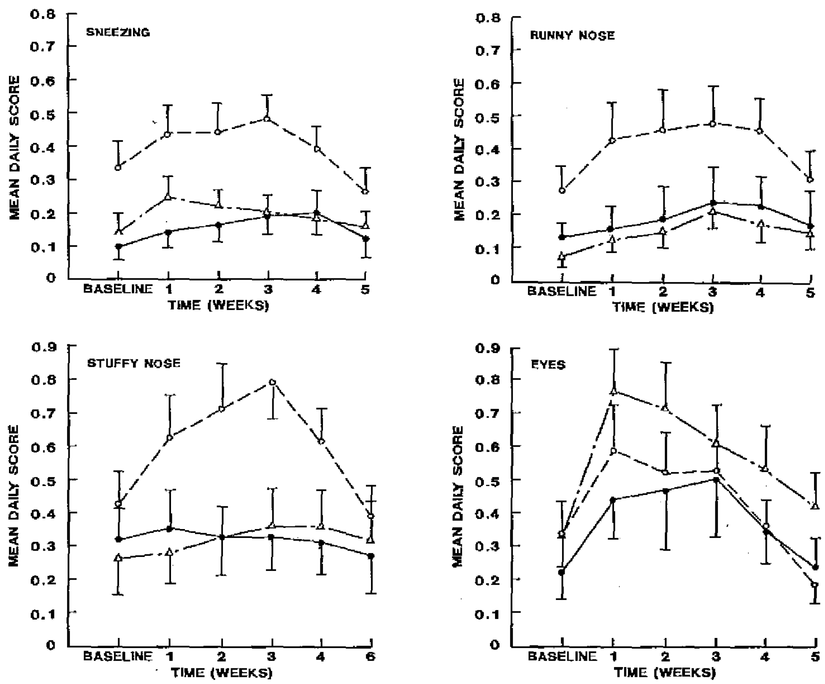


FIG. 1. Mean daily nose and eye symptom scores (SEM) before and throughout the ragweed-pollen season; astemizole alone (○); aqueous beclomethasone nasal spray alone (△); astemizole plus aqueous beclomethasone nasal spray (●).

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

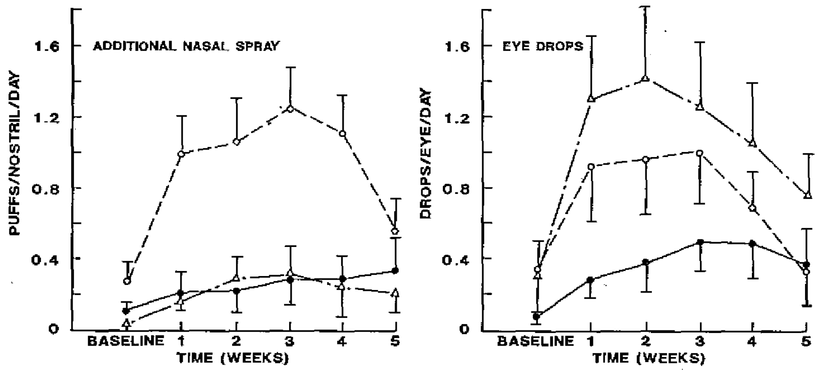


FIG. 2. Mean daily additional medication use (SEM) before and throughout the ragweed-pollen season; astemizole alone (○); aqueous beclomethasone nasal spray alone (△); astemizole plus aqueous beclomethasone nasal spray (●).

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.

REFERENCES

1. Mygind N. Nasal allergy. Oxford: Alden Press, 1978:257-9.
2. Mygind N. Nasal allergy. Oxford: Alden Press, 1978:312-7.
3. Sibbald B, Hilton S, D'Souza M. An open crossover trial comparing two doses of astemizole and beclomethasone dipropionate in the treatment of perennial rhinitis. Clin Allergy 1986;16:203-11.
4. Munch EP, Soborg M, Norreslet TT, Mygind N. A comparative study of dexchlorpheniramine maleate sustained-release tablets and budesonide nasal spray in seasonal allergic rhinitis. Allergy 1983;38:517-24.
5. Beswick KBJ, Kenyon GS, Cherry JR. A comparative study of beclomethasone dipropionate aqueous nasal spray with terfenadine tablets in seasonal allergic rhinitis. Curr Med Res Opin 1985;9:560-7.
6. Dickson DJ, Cruickshank JM. Comparison of flunisolide nasal spray and terfenadine tablets in hay fever. Br J Clin Pract 1984;38:416-20.
7. Wood SF. Oral antihistamine or nasal steroid in hay fever: a double-blind double-dummy comparative study of once-daily oral astemizole vs twice-daily nasal beclomethasone dipropionate. Clin Allergy 1986;16:195-201.
8. Dunn AM, Wilson RSE, Baggott PJ. A comparison of beclomethasone dipropionate aqueous nasal spray and beclomethasone dipropionate pressurized nasal spray in the management of seasonal rhinitis. Postgrad Med J 1984:60:404-6.
9. Brogden RN, Heel RC, Speight TM, Avery GS. Beclomethasone dipropionate: a reappraisal of its pharmacodynamic properties and therapeutic efficacy after a decade of use in asthma and rhinitis. Drugs 1984;28:99-126.
10. Howarth PH, Emanual MB, Holgate ST. Astemizole, a potent histamine H_1-receptor antagonist: effect in allergic rhinoconjunctivitis on allergen and histamine-induced skin wheal responses, and relationship to serum levels. Br J Clin Pharmacol 1984;18:1-8.
11. Juniper EF, Cartier A, Trebilcock AL, Frith PA, Dolovich J, Hargreave FE. Effects of oxatomide compared with chlorpheniramine in allergic rhinoconjunctivitis. Clin Allergy 1981; 11:61-6.
12. Kleinbaum DG, Kupper LL. Applied regression analysis and other multivariable methods. Boston: Duxbury Press, 1978: 264-77.
13. Juniper EF, White J, Dolovich J. Efficacy of continuous treatment with astemizole (Hismanal) and terfenadine (Seldane) in ragweed pollen–induced rhinoconjunctivitis. J Allergy Clin Immunol 1988;82:670-5.
14. Straus SE, Dale JK, Wright R, Metcalfe DD. Allergy and the chronic fatigue syndrome. J Allergy Clin Immunol 1988; 81:791-5.
15. Howarth PH, Holgate ST. Comparative trial of two nonsedative H_1 antihistamines, terfenadine and astemizole, for hay fever. Thorax 1984;39:668-72.
16. Wood SF. Astemizole and terfenadine compared in hay fever. Practitioner 1986;230:41-4.
17. Wihl J-A, Petersen BN, Petersen LN, Gundersen G, Bresson K, Mygind N. Effect of the nonsedative H_1-receptor antagonist astemizole in perennial allergic and nonallergic rhinitis. J Allergy Clin Immunol 1985;75;720-7.

Exhibit D

WISCONSIN | Information Retrieval For Business and Industry

TECH SEARCH

WTS Number: 678750

678750

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

Washington, DC 20005

RUSH

Company Phone: 202-371-2600

Requester Phone: 202-772-8789

Fax: 202-371-2540

Requester Email: Tjones@skgf.com

Send-To Email: Tjones@skgf.com

Reference: 2286.0030002

Delivery: Email

Instructions:

2}Ratner et al., J. Fam. Pract. 47(2):118-125 (1998);

Med
Q
7J8163
F2

0094-3509

An outreach service of the Kurt F. Wendt Library, University of Wisconsin - Madison
Email: wts@engr.wisc.edu | Web: http://www.wisc.edu/techsearch | Phone: (608) 262-5917

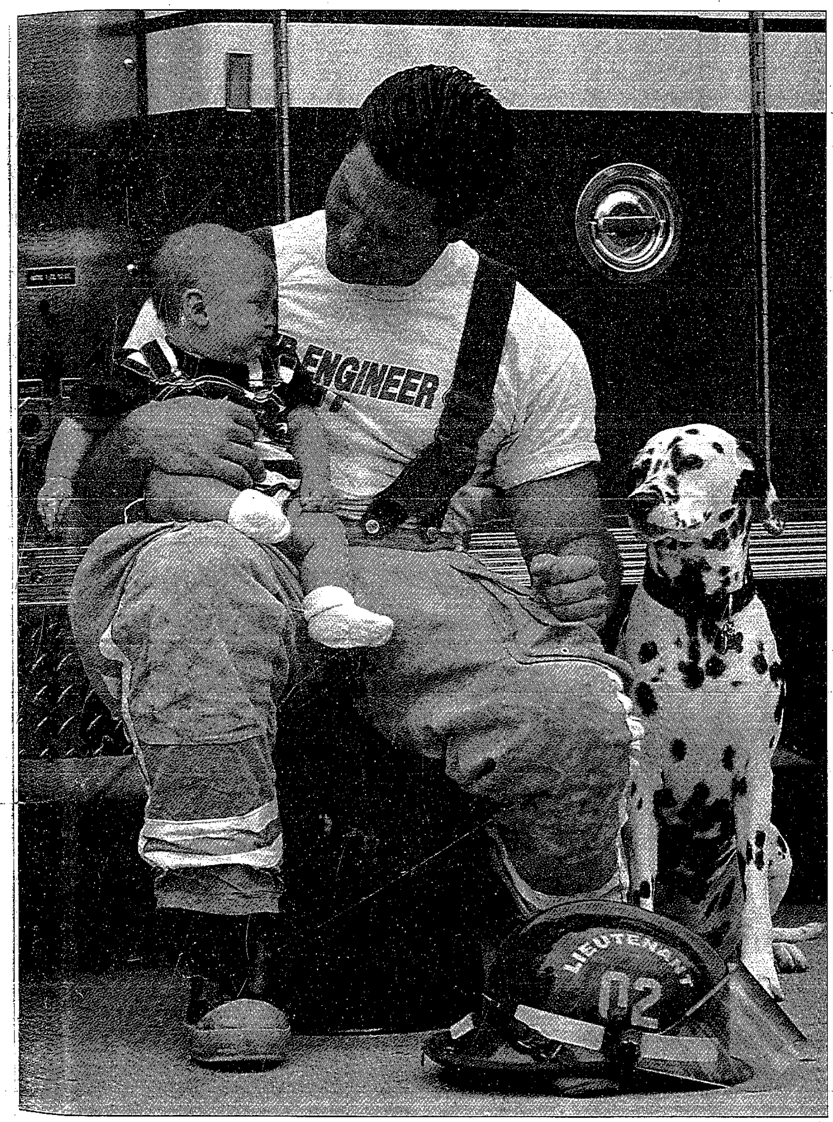
Requester assumes responsibility for copyright compliance.

Refer Off Campus

LTL

THE JOURNAL OF
FAMILY PRACTICE

July 1998 Volume 47 Number 1



APPLETON & LANGE
A Simon & Schuster Company

THE JOURNAL OF
FAMILY PRACTICE

Archival Services
The Journal of Family Practice is indexed in the following: Index Medicus, Current Contents (Clinical Medicine), Science Citation Index, Cambridge Scientific Abstracts, EMBASE/Excerpta Medica, International Pharmaceutical Abstracts, PsycINFO/Psychological Abstracts and the Cumulative Index to Nursing and Allied Health Literature. The Journal is also available in microform from University Microfilms, Ann Arbor, Michigan.

Copyright

Permissions Policy
Authorization to photocopy articles in this publication for internal or personal use, or for the internal or personal use of specific clients, is granted by Appleton & Lange to libraries and other users registered with the Copyright Clearance Center (CCC) Transactional Reporting Service, provided that a fee of $3.00 per article is paid directly to:

CCC
222 Rosewood Dr
Danvers, MA 01923
Telephone (508) 750-8400
FAX (508) 750-4744
0094-3509/97/ + $3.00/ + 0

This consent does not apply to other kinds of copying, such as copying for general distribution, for advertising or promotional purposes, for creating new collective works, or for resale. Such permission requests, and other inquires, should be addressed to the Publisher.

Reprints
Authorized reprints may be purchased in quantities of 100 or more. For smaller quantities, back issues may be purchased at the single copy rate. For prices and ordering information, contact Reprints Coordinator, Appleton & Lange, PO Box 120041, Stamford, CT 06912-0041: telephone (203) 406-4616; FAX (203) 406-4603.

Editorial and Advertising Policy
Statements and opinions expressed in articles and communications herein are those of the author(s) and not necessarily those of the Editor, Publisher, or any organizations endorsing this journal. Neither the Editor, Publisher, nor organizations endorsing this journal guarantee, warrant, or endorse any product or service advertised in this journal, nor do they guarantee any claim made by the manufacturer of such product or service.

Cover Photo
George Shelley @ 1997/The Stock Market

ORIGINAL RESEARCH

A Comparison of the Efficacy of Fluticasone Propionate Aqueous Nasal Spray and Loratadine, Alone and in Combination, for the Treatment of Seasonal Allergic Rhinitis

Paul H. Ratner, MD; Julius H. van Bavel, MD; Bruce G. Martin, DO; Frank C. Hampel, Jr., MD; William C. Howland, III, MD; Paula R. Rogenes, PhD; Ronald E. Westlund; Brian W. Bowers, PharmD; and Cindy K. Cook

San Antonio, Austin, and New Braunfels, Texas; and Research Triangle Park, North Carolina

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 $\leq .05$. 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.

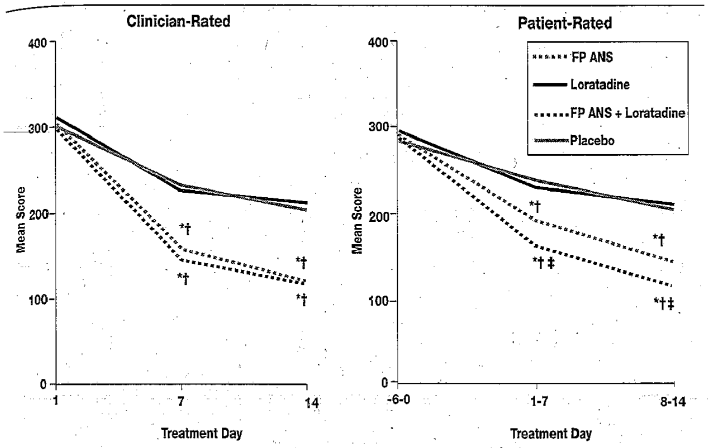
RESULTS

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.

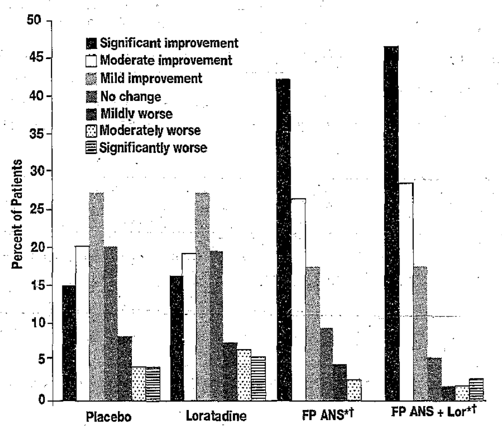
Efficacy Data

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

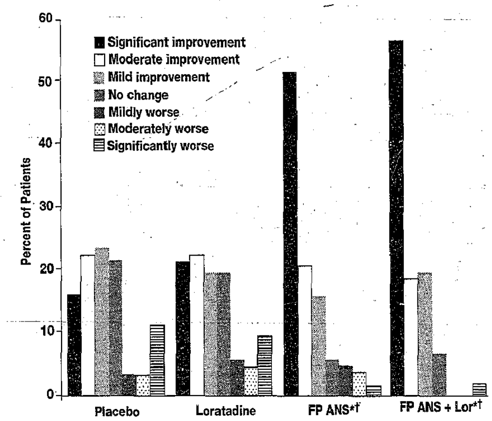
Clinician-rated overall response to therapy after 2 weeks of therapy for seasonal allergic rhinitis.



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.

ACKNOWLEDGMENTS

This study was supported by a grant from Glaxo Wellcome Inc. We would like to thank Gary Pakes, PharmD, for his assistance in the preparation of this manuscript.

REFERENCES

1. Bousquet J, Dhivert H, Michel F-B. Current trends in the management of allergic diseases. Allergy 1994; 94:31-6.
2. Horak F. Seasonal allergic rhinitis. Newer treatment approaches. Drugs 1993; 45:518-27.
3. Brogden RN, Pinder RM, Sawyer PR, Speight TM, Avery GS. Beclomethasone dipropionate. II. Allergic rhinitis and other conditions. Drugs 1975; 10:211-38.
4. Phillipps GH. Structure-activity relationships of topically active steroids: the selection of fluticasone propionate. Respir Med 1990; 84(suppl A):19-23.
5. Harding SM. The human pharmacology of fluticasone propionate. Respir Med 1990; 84(suppl A):25-29.
6. Howland WC III, Hampel FC Jr., Martin BG, Ratner PH, van Bavel JH, Field EA. The efficacy of fluticasone propionate aqueous nasal spray for allergic rhinitis and its relationship to topical effects. Clin Ther 1996; 18:1106-17.
7. Howland WC III. Fluticasone propionate: topical or systemic effects? Clin Exp Allergy 1996; 26(suppl 3):18-22.
8. Nayak AS, Shulan D, Bernstein DI, et al. Intranasal fluticasone propionate (FP) is more effective than loratadine (LOR) for treatment of seasonal allergic rhinitis symptoms [abstract 63]. J Allergy Clin Immunol 1996; 97:198.
9. Ramsdale HE, Kline PA. Comparison of once daily treatment with an antihistamine (loratadine) and topical steroid (fluticasone propionate) during the ragweed pollen season [abstract 636]. J Allergy Clin Immunol 1991; 87(suppl):298.
10. Gehanno P, Desfougeres JL. Fluticasone propionate aqueous nasal spray compared with oral loratadine in patients with seasonal allergic rhinitis. Allergy 1997; 52:445-50.

11. Jordana G, Dolovich J, Briscoe MP, et al. Intranasal fluticasone propionate versus loratadine in the treatment of adolescent patients with seasonal allergic rhinitis. J Allergy Clin Immunol 1996; 97:588-95.
12. van Bavel J, Findlay S, Hampel F, et al. Intranasal fluticasone propionate is more effective than terfenadine tablets for seasonal allergic rhinitis. Arch Intern Med 1994; 154:2699-2704.
13. Darnell R, Pecoud A, Richards DH. A double-blind comparison of fluticasone propionate aqueous nasal spray, terfenadine tablets and placebo in the treatment of patients with seasonal allergic rhinitis to grass pollen. Clin Exp Allergy 1994; 24:1144-50.
14. Bronsky EA, Dockhorn RJ, Meltzer EO, et al. Fluticasone propionate aqeuous nasal spray compared with terfenadine tablets in the treatment of seasonal allergic rhinitis. J Allergy Clin Immunol 1996; 97:915-21.
15. Stricker WE, Klimas JT, Mendelson L, et al. Intranasal fluticasone propionate is more effective than astemizole for seasonal allergic rhinitis [abstract P34]. Ann Allergy 1994; 72:86.
16. Vervloet D, Charpin D, Desfougeres J-L. Intranasal fluticasone once daily compared with once-daily cetirizine in the treatment of seasonal allergic rhinitis. Clin Drug Invest 1997; 13:291-8.
17. Drouin MA, Yang WH, Horak F, et al. Is there a benefit to adding loratadine to topical nasal steroids in patients with moderately severe seasonal allergic rhinoconjunctivitis? [abstract]. Allergy 1992; 12(suppl):173.
18. Wihl JA, Nuchel Petersen B, Nuchel Peterson L, et al. Effect of the nonsedative H1-receptor antagonist astemizole in perennial allergic and nonallergic rhinitis. J Allergy Clin Immunol 1985; 75:720-7.
19. Jarmoszuk I, LeFach J, Hogan A. Dual therapy for seasonal allergic rhinitis (SAR) with terfenadine (T) and beclomethasone nasal aerosol (B) [abstract]. J Allergy Clin Immunol 1986; 77(suppl):138.
20. Benincasa C, Lloyd RS. Evaluation of fluticasone propionate aqueous nasal spray taken alone and in combination with cetirizine in the prophylactic treatment of seasonal allergic rhinitis. Drug Invest 1994; 8:225-33.
21. Linder A. Symptom scores as measures of the severity of rhinitis. Clin Allergy 1988; 18:29-37.
22. Juniper EF, Guyatt GH. Development and testing of a new measure of health status for clinical trials in rhinoconjunctivitis. Clin Exp Allergy 1991; 21:77-83.
23. Cox FM, Bowers BW, Ratner PH, Cook CK, Westlund R, Rogenes PR. The effect of fluticasone propionate aqueous nasal spray and loratadine, alone and in combination, on pharmacoeconomic outcomes in patients with seasonal allergic rhinitis. J Managed Care Pharm. In press.
24. Olsen OT, Nüchel Petersen LN, Høi L, Lorentzen KA, Hindberg Rasmussen W, Svendsen UG. Comparison of loratadine and terfenadine in allergic seasonal rhinoconjunctivitis with emphasis on nasal stuffiness and peak flow. Arzneimittelforschung 1992; 42:1227-31.
25. Mackowiak JI. Fluticasone propionate aqueous nasal spray (FP) improves rhinitis quality of life and reduces lost labor costs [abstract P86]. Ann Allergy 1994; 72:99.
26. Lemanske R, Dunn K, Galant S, et al. Fluticasone propionate aqueous nasal spray is more effective than astemizole in the treatment of seasonal allergic rhinitis [abstract 15]. J Allergy Clin Immunol 1994; 93:165.
27. Bousquet J. Clinical activity and side effects of loratadine and astemizole in patients with seasonal allergic rhinitis [abstract]. Presented at the 44th Annual Congress of the American College of Allergists; Boston, Mass, November 1987.
28. Oei HD. Double-blind comparison of loratadine (SCH 29851), astemizole, and placebo in hay fever with special regard to onset of action. Ann Allergy 1988; 61:436-9.
29. Del Carpio J, Kabbash L, Turenne Y, et al. Efficacy and safety of loratadine (10 mg once daily), terfenadine (60 mg twice daily), and placebo in the treatment of seasonal allergic rhinitis. J Allergy Clin Immunol 1989; 84:741-6.
30. Horak F, Bruttmann G, Pedrali P, et al. A multicentre study of loratadine, terfenadine and placebo in patients with seasonal allergic rhinitis. Arzneimittelforschung 1988; 38:124-8.
31. Meltzer EO, Schatz M. Pharmacotherapy of rhinitis: 1987 and beyond. Immunol Allergy Clin North Am 1987; 7:57-91.
32. Brompton Hospital/Medical Research Council Collaborative Trial. Double-blind trial comparing two dosage schedules of beclomethasone dipropionate aerosol with a placebo in the treatment of perennial rhinitis for twelve months. Clin Allergy 1980; 10:239-51.
33. Schenkel EJ, Nolop R, Mesarina-Wicki B. Evaluation of mometasone furoate (NasonexTM) nasal spray with the addition of loratadine vs a placebo in the treatment of seasonal allergic rhinitis [abstract]. Presented at the American College of Allergy, Asthma and Immunology 1996 Annual Meeting, Boston, Mass, November 8-13, 1996.
34. Nathan RA, Bronsky EA, Firemen P, et al. Once daily fluticasone propionate aqueous nasal spray is an effective treatment for seasonal allergic rhinitis. Ann Allergy 1991; 67:332-8.

Exhibit E

WISCONSIN | Information Retrieval For Business and Industry

TECH SEARCH

WTS Number: 678751

678751

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

Washington, DC 20005

RUSH

Company Phone: 202-371-2600

Requester Phone: 202-772-8789

Fax: 202-371-2540

Requester Email: Tjones@skgf.com

Send-To Email: Tjones@skgf.com

Reference: 2286.0030002

Delivery: Email

Instructions:

---

3)Simpson, R. J., Ann. Allergy 73(6):497-502 (1994);

Med
φ
7AN59

0003-4738

Refer Off Campus

ANNALS OF ALLERGY
Devoted to the Interests of the Practicing Allergist
December, 1994
Volume 73, Number 6

CME CREDIT Review Article and Questions—See Pages 457–469

Review Article

Clinical Allergy-Immunology Rounds

Original Articles

ANNALS OF ALLERGY

Editor: R. Michael Sly, MD
Children's National Medical Center
111 Michigan Ave. NW
Washington, DC 20010-2970
Tel: (202) 884-3136
Office hours: Mon and Wed:
7:30 AM to 4 PM SDT
Thurs: Noon to 4:30 PM

The Annals of Allergy is the Official Publication of the American College of Allergy and Immunology and is devoted to the interests of the practicing allergist

December, 1994

REVIEW ARTICLE

CLINICAL ALLERGY-IMMUNOLOGY ROUNDS

ORIGINAL ARTICLES

(Continued on page A-6)

For submission of articles, see "Instructions for Authors"
Changes of address directed to the ANNALS OF ALLERGY should be sent to Jim Slawny, Executive Director
***ANNALS OF ALLERGY*, Suite 550**
85 West Algonquin Road, Arlington Heights
Illinois 60005
Telephone—(708) 427-1200

***Annals of Allergy* (ISSN-0003-4738) is published monthly for $42.50 (US), $55.00 (US institutions) and $68.00 (foreign) by the American College of Allergy and Immunology, 7212 Davis Ct, McLean, VA 22101. Second class postage paid at McLean, VA and additional mailing offices. (POSTMASTER: Send address changes to AMERICAN COLLEGE OF ALLERGY AND IMMUNOLOGY, 85 West Algonquin Road, Suite 550, Arlington Heights, IL 60005.) Printed in the USA.**

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

From the Forth Valley GP Research Group, Department of Clinical Psychology, University of Stirling, Stirling, UK.

This study was supported by a grant from Astra Draco AB, Lund, Sweden.

Received for publication February 22, 1994.

Accepted for publication in revised form July 6, 1994.

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

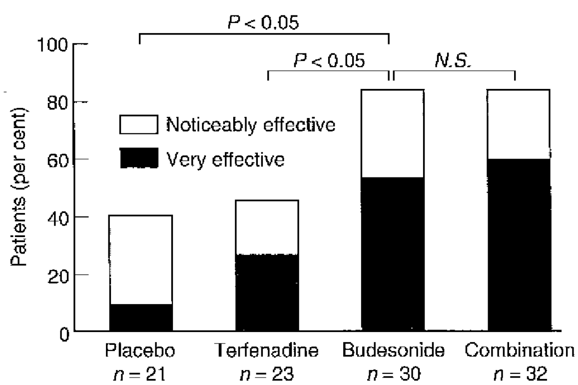


Figure 1. Patients' overall assessment of the efficacy of treatment. Percentage of patients in each treatment group who reported the global efficacy of their treatment at week 3 as noticeably effective or very effective, with statistical comparison between groups (Wilcoxon rank sum-W test). NS = not 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

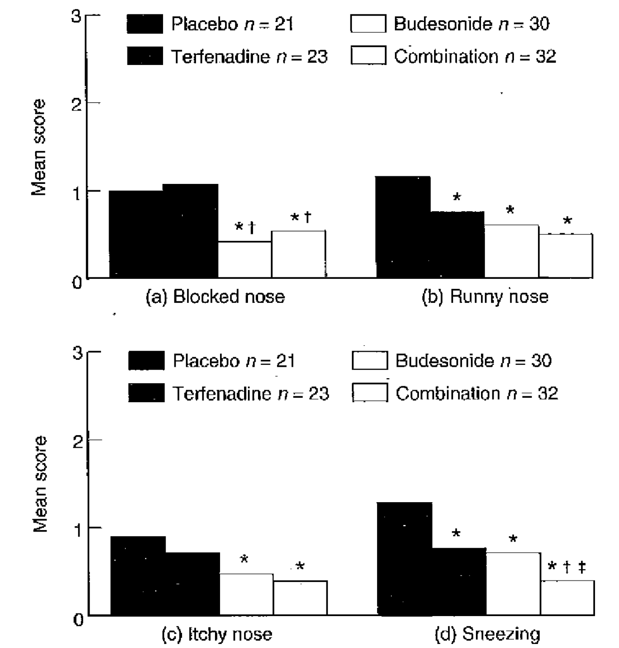


Figure 2. Assessment of nasal symptom scores at week 3 as derived from patients' diary booklets. * Statistically significant difference versus placebo ($P < .05$). † Statistically significant difference versus terfenadine ($P < .05$). ‡ Statistically significant difference versus budesonide ($P < .05$).

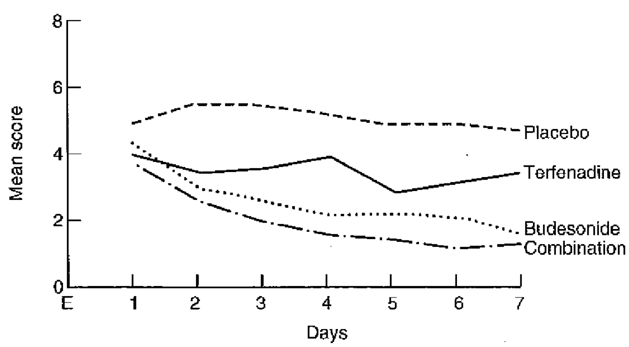


Figure 3. Changes in mean total nasal symptom scores in each treatment group during the first week of treatment.

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.

ACKNOWLEDGMENTS

The author would like to acknowledge the work of the General Practitioner members of the Forth Valley GP Research Group, and the assistance of Mrs V. Swanson, Research Administrator.

REFERENCES

1. Broder I, Barlow PP, Hortin RJM. The epidemiology of asthma and hay fever in a total community, Tecumseh, Michigan. J Allergy Clin Immunol 1974;54:100–10.
2. Kaliner M, Eggleston P, Mathews K. Rhinitis and asthma. JAMA 1987;258:2851–73.
3. Lemanske RF, Kaliner M. Late phase allergic reactions. In: Middleton E, Reed CE, Ellis EF, Adkinson NF Jr, Yunginger JW, eds. Allergy: principles and practice, 3rd ed. St Louis: The CV Mosby Co, 1988: 224–46.
4. Orgel HA, Meltzer EO, Kemp JP, et al. Comparison of intranasal cromolyn sodium, 4% and oral terfenadine for allergic rhinitis: symptoms, nasal cytology, nasal ciliary clearance and rhinomanometry. Ann Allergy 1991;66:237–44.
5. Hillas J, Booth RJ, Somerfield S, et al. A comparative trial of intranasal beclomethasone dipropionate and sodium cromoglycate in patients with chronic perennial rhinitis. Clin Allergy 1980;10:253–8.
6. Brown E, Seideman T, Siegelaub AB, et al. Depo-methylprednisone in the treatment of ragweed hay fever. Ann Allergy 1960;18: 1321–30.
7. Norman PS, Kunkel G, Weeke B, eds. Allergic and vasomotor rhinitis: clinical aspects. Copenhagen: Munksgaard 1986:132–9.
8. Kaliner MA, Check WA. Non-sedating antihistamines. Allergy Proc 1988;9:649–63.
9. Simons FER, Kesselman MS, Giddins NG, et al. Astemizole-induced torsades de pointes. Lancet 1988;2: 624.
10. Davies AJ, Harinda V, McEwan A, et al. Cardiotoxic effect with convulsions in terfenadine overdose. Br Med J 1989;298:325.
11. Monahan BP, Ferguson CL, Killeavy ES, et al. Torsade de pointes occurring in association with terfenadine use. JAMA 1990;264: 2788–90.
12. Estelle F, Simons R. Antihistamines. In: Mygind N, Naclerio RM, eds. Allergic and non-allergic rhinitis. Clinical aspects. Copenhagen: Munksgaard, 1993:123–36.
13. Ganderton MA, James VHT. Clinical and endocrine side-effects of methylprednisolone acetate as used in hay fever. Br Med J 1970;1: 267–9.
14. Welsh PW, Stricker WE, Chu-Pin C, et al. Efficacy of beclomethasone nasal solution, flunisolide, and cromolyn in relieving symptoms of ragweed allergy. Mayo Clinic Proc 1987;62:125–34.
15. Schleimer RP. Glucocorticosteroids. In: Middleton E, Reed CE, Ellis EF, Adkinson NF Jr, Yunginger JW, eds. Allergy: principles and practice, 3rd ed. St Louis: The CV Mosby Co, 1988:739–65.
16. Naclerio RM, Mygind N. Intranasal steroids. In: Mygind N, Naclerio RM, eds. Allergic and non-allergic rhinitis. Clinical aspects. Copenhagen: Munksgaard, 1993:114–22.
17. Cameron AW, Stanley IM, Wright HJ. Randomized double blind controlled clinical trial of intranasal budesonide in treatment of hay fever. Br Med J 1984;288:1881–4.
18. Backhouse CI, Brewster BS, Lockhart JDF, et al. Terfenadine in allergic rhinitis: a comparative trial of a new antihistamine versus chlorpheniramine and placebo. Practitioner 1982;226:347–51.
19. Howarth PH, Holgate ST. Comparative trial of two non-sedative H_1 antihistamines, terfenadine and astemizole, for hay fever. Thorax 1984;39:668–72.
20. Dickson DJ, Cruikshank JM. Comparison of flunisolide nasal spray and terfenadine tablets in hay fever. Br J Clin Pract 1984;11/12: 416–20.

21. Spector SL, Toshener D, Gay I, et al. Beneficial effects of propylene and polyethylene glycol and saline in the treatment of perennial rhinitis. Clin Allergy 1982;12:187–96.
22. McArthur JG, Higgins AJ. A comparison of budesonide and BDP aqueous sprays in the treatment of hay fever [Abstract]. Allergy 1988; 43(Suppl 7):114.
23. Vanzielegheim MA, Juniper EF. A comparison of budesonide and beclomethasone dipropionate nasal aerosols in ragweed-induced rhinitis. J Allergy Clin Immunol 1987; 79:887–92.

Request for reprints should be addressed to:
Richard J Simpson, MB, ChB
Forth Valley GP Research Group
Dept. Psychology
University of Stirling
Stirling FK9 4LA UK

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.

Exhibit F

Allergy 2000: 62: 6-11

ALLERGY
ISSN 0108-1675

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.

P. H. Howarth
Division of Respiratory Cell and Molecular Biology Research, University of Southampton School of Medicine, Southampton, UK

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

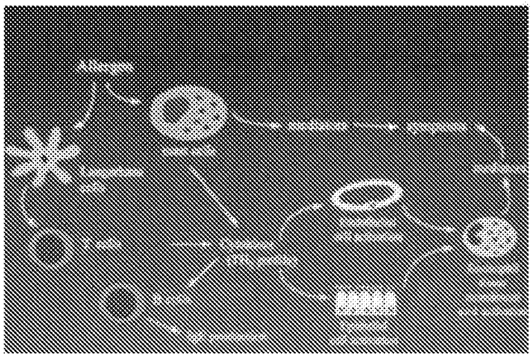


Figure 1. Allergic airways inflammation.

(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).

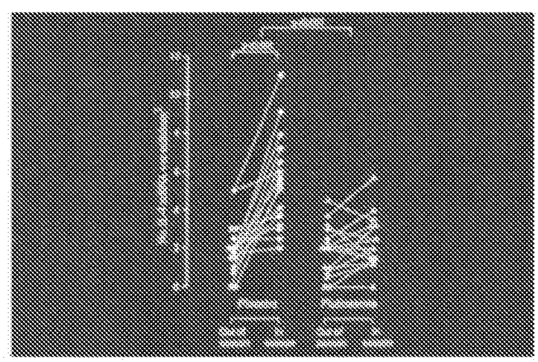


Figure 2. Influence of fluticasone propionate on mucosal IL-4 mRNA in nasal biopsies in seasonal allergic rhinitis (Cameron et al. [17]).

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).

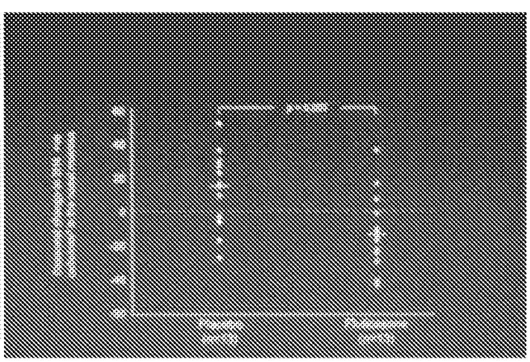


Figure 3. Influence of prophylactic fluticasone propionate on IL-4 secretion by mast cells in seasonal allergic rhinitis (Bradding et al. [19]).

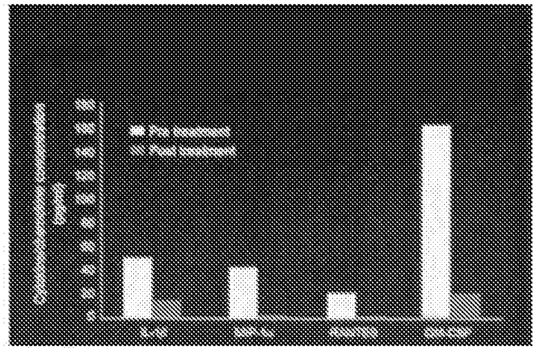


Figure 4. Nasal lavage chemokine levels: influence of fluticasone propionate (Weido et al. [22]).

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.

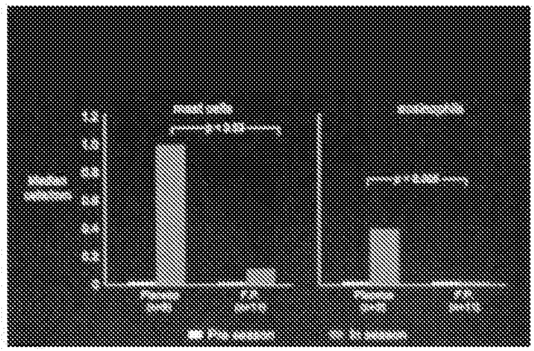


Figure 5. Epithelial eosinophil and mast-cell accumulation in seasonal allergic rhinitis: influence of prophylactic fluticasone propionate, 200 µg once daily (Bradding et al. [19]).

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.

References

1. Howarth PH. ABC of allergies: pathogenic mechanisms: a rational basis for treatment. BMJ 1998;**316**:758–761.
2. Bradding P, Feather IH, Wilson S, Bardin P, Holgate ST, Howarth PH. Immunolocalisation of cytokines in the nasal mucosa of normal and perennial rhinitis subjects: the mast cell as a source of IL-4, IL-5 and IL-6 in human allergic inflammation. J Immunol 1993;**151**:3853–3865.
3. Bentley AM, Jacobson MR, Cumberworth B, et al. Immunohistology of the nasal mucosa in seasonal allergic rhinitis: increases in activated eosinophils and epithelial mast cells. J Allergy Clin Immunol 1992;**89**:821–829.
4. Okuda M, Otsuka H, Kawabori S. Studies on nasal surface basophilic cells. Ann Allergy 1995;**55**:69.
5. Wilson S, Lau L, Howarth PH. Inflammatory mediators in naturally occurring rhinitis. Clin Exp Allergy 1998;**28**:220–227.
6. Montefort S, Holgate ST, Howarth PH. Leucocyte-endothelial adhesion molecules and their role in bronchial asthma and allergic rhinitis. Eur Respir J 1993;**6**:1044–1054.
7. Teran M, Davis DE. The chemokines: their potential role in allergic inflammation. Clin Exp Allergy 1996;**26**:1005–1019.
8. Barnes PJ. Nuclear factor-kappa B. Int J Biochem Cell Biol 1997;**29**:867–870.
9. Baeuerle PA, Baltimore D. IκB: a specific inhibitor of the NF-κB transcription factor. Science 1988;**242**:540–546.
10. Barnes PJ, Adcock IM. Anti-inflammatory actions of steroids: molecular mechanisms. Trends Pharmacol Sci 1993;**14**:436–441.
11. English AF, Neate MS, Quint DJ, Sareen M. Biological activities of some steroids used in asthma. Am J Respir Crit Care Med 1994;**149**:A4.
12. Landwehr LP, Spahn JD, Kamanda AK, Surs W, Leung DYM, Szefler SJ. Effects of hydrocortisone and synthetic glucocorticoids on lymphocyte activation in steroid-resistant asthmatics. J Allergy Clin Immunol 1995;**95**:988.
13. Umland SP, Nahrebne DK, Razac S, et al. The inhibitory effects of topically active glucocorticoids on IL-4, IL-5 and interferon gamma production by cultured primary CD4+ T cells. J Allergy Clin Immunol 1997;**100**:511–519.
14. McConnell W, Howarth PH. The airway anti-inflammatory effects of fluticasone propionate. Rev Contemp Pharmacother 1998;**9**:523–533.
15. Hagaman DD, Bridges TA, Serafin WE. Glucocorticoids inhibit cytokine production by human and murine mast cells. J Allergy Clin Immunol 1995;**95**:298.
16. Fuller R, Johnson M, Bye A. Fluticasone propionate – an update on preclinical and clinical experience. Respir Med 1995;**89** Suppl A:3–18.
17. Cameron LA, Durham SR, Jacobson MR, et al. Expression of IL-4, Cepsilon RNA, and Iepsilon RNA in the nasal mucosa of patients with seasonal rhinitis: effect of topical corticosteroids. J Allergy Clin Immunol 1998;**101**:330–336.
18. Masuyama K, Till SJ, Jacobson MR, et al. Nasal eosinophilia and IL-5 mRNA expression in seasonal allergic rhinitis induced by natural allergen exposure: effect of topical corticosteroids. J Allergy Clin Immunol 1998;**102**:610–617.
19. Bradding P, Feather IH, Wilson S, Holgate ST, Howarth PH. Cytokine immunoreactivity in seasonal rhinitis: regulation by a topical corticosteroid. Am J Respir Crit Care Med 1995;**151**:1900–1906.
20. Montefort S, Feather I, Wilson S, Haskard DO, Howarth PH. Endothelial leucocyte adhesion molecule expression in seasonal allergic rhinitis: relevance to disease expression and regulation by topical fluticasone propionate therapy. Eur Respir J 1993;**6 Suppl 17**:123.
21. Holm A, Fokkens W, Godthelp T, Vroom T, Rijntjes E. Safety and efficacy of one-year treatment with fluticasone propionate on clinical signs and inflammatory cells in the nasal mucosa of allergic perennial rhinitis patients. Allergologie 1996;**19**:43.
22. Weido AJ, Reece LM, Alam R, Cook CK, Sim TC. Intranasal fluticasone propionate inhibits recovery of chemokines and other cytokines in nasal secretions in allergen-induced rhinitis. Ann Allergy Asthma Immunol 1996;**77**:407–415.
23. Howarth PH. Clinical efficacy of H_1-antihistamine. Clin Exp Allergy 1999;**29 Suppl 3**:87–97.
24. Church MK, Gradidge CF. Inhibition of histamine release from human lung *in vitro* by antihistamines: their effect on the mast cell. Br J Pharmacol 1960;**15**:398–404.
25. Little MM, Casale TB. Azelastine inhibits IgE-mediated human basophil histamine release. J Allergy Clin Immunol 1989;**83**:862–865.
26. Church MK, Gradidge CF. Oxatomide: inhibition and stimulation of histamine release from human lung and leucocytes *in vitro*. Agents Actions 1980;**10**:4–7.

27. Okayama Y, Church MK. Comparisons of the modulatory effect of ketotifen, sodium cromoglycate, procaterol and salbutamol in human skin, lung and tonsil mast cells. Int Arch Allergy Immunol 1992;**97**:216–225.
28. Kreutner W, Chapman RW, Gulbelkian A, Siegel MI. Antiallergic activity of loratadine, a non-sedating antihistamine. Allergy 1987;**42**:57–63.
29. Seeman P. The membrane actions of anaesthetics and tranquilizers. Pharmacol Rev 1972;**24**:583–655.
30. Peachell PT, Pearce FL. Effect of calmodulin inhibitors on histamine secretion from mast cells. Agents Actions 1985;**16**:43–44.
31. Berthon B, Taudou G, Combettes L, et al. *In vitro* inhibition of loratadine and descarboxyethoxyloratadine, of histamine release from human basophils and of histamine release and intracellular calcium fluxes in rat basophilic leukaemia cells. Biochem Pharmacol 1994;**47**:789–794.
32. Canonica GW, Ciprandi G, Buscaglia S, Pesce G, Bagnasco M. Adhesion molecules of allergic inflammation: recent insights into their functional roles. Allergy 1994;**49**:135–141.
33. Baroody FM, Lim MC, Proud D, Kagey-Sobotka A, Lichtenstein LM, Naclerio RM. Effects of loratadine and terfenadine on the induced nasal allergic reaction. Arch Otolaryngol Head Neck Surg 1996;**122**:309–316.
34. Shin M-H, Baroody F, Proud D, Kagey-Sobotka A, Lichtenstein LM, Naclerio RM. The effect of azelastine on the early allergic response. Clin Exp Allergy 1992;**22**:289–295.
35. Naclerio RM, Proud D, Kagey-Sobotka A, Freidhoff L, Norman PS, Lichtenstein LM. The effect of cetirizine on early allergic response. Laryngoscope 1989;**99**:596–599.
36. Majchel AM, Proud D, Kagey-Sobotka A, Lichtenstein LM, Naclerio RM. Ketotifen reduces sneezing but not histamine release following nasal challenge with antigen. Clin Exp Allergy 1990;**20**:701–705.
37. Bousquet J, Lebel B, Chanal I, Morel A, Michel FB. Antiallergic activity of H_1-receptor antagonists assessed by nasal priming. J Allergy Clin Immunol 1989;**84**:492–501.
38. Andersson M, Nolte H, Baumgartem C, Pipkorn U. Suppressive effect of loratadine on allergen-induced histamine release in the nose. Allergy 1991;**46**:540–546.
39. Naclerio RM, Kagey-Sobotka A, Lichtenstein LM, Freidhoff L, Proud D. Terfenadine, an H_1-antihistamine, inhibits histamine release *in vivo* in the human. Am Rev Respir Dis 1990;**142**:167–171.
40. Klementsson H, Andersson M, Pipkorn U. Allergen-induced increase in non-specific nasal reactivity is blocked by antihistamines without a clear-cut relationship to eosinophil influx. J Allergy Clin Immunol 1990;**86**:466–672.
41. Meyer P, Persson CG, Andersson M, et al. Alpha 2-macroglobulin and eosinophil cationic protein in the allergic airway mucosa in seasonal allergic rhinitis. Eur Respir J 1999;**13**:633–632.
42. Bruttman G, Arendt C, Bernheim J. Double-blind, placebo-controlled comparison of cetirizine and terfenadine in atopic perennial rhinitis. Acta Ther 1989;**15**:99–109.
43. Zetterström E, Halopainen E, Johnson C. Efficacy and tolerability of cetirizine and terfenadine in the treatment of perennial allergic rhinitis (PAR). Allergy 1992;**47**:179.
44. Charlesworth EN, Kagey-Sobotka A, Norman PS, Lichtenstein LM. Effect of cetirizine on mast cell mediator release and cellular traffic during cutaneous late phase reaction. J Allergy Clin Immunol 1989;**83**:905–912.
45. Ciprandi G, Tosca M, Ricca V, et al. Cetirizine treatment of rhinitis in children with pollen allergy: evidence of its antiallergic activity. Clin Exp Allergy 1996;**27**:1160–1166.
46. Wang D, Clement P, Smitz J. Effect of H_1 and H_2 antagonists on nasal symptoms and mediator release in atopic patients after nasal allergen challenge during the pollen season. Acta Otolaryngol (Stockh) 1996;**116**:91–96.
47. Howarth PH, Wilson SJ, Brewster H. The influence of cetirizine on nasal eosinophilia in seasonal allergic rhinitis. J Allergy Clin Immunol 1991;**87**:151.
48. Fasce L, Ciprandi G, Pronzato C, et al. Cetirizine reduces ICAM-1 on epithelial cells during nasal minimal persistent inflammation in asymptomatic children with mite-allergic asthma. Int Arch Allergy Immunol 1996;**109**:272–276.
49. Howarth PH, Holgate ST. Comparative trial of two non-sedative H_1-antihistamines, terfenadine and astemizole for hay fever. Thorax 1984;**39**:668–672.
50. Welsh PW, Stricker WE, Chu CP, et al. Efficacy of beclomethasone nasal solution, flunisolide, and cromolyn in relieving symptoms of ragweed allergy. Mayo Clin Proc 1987;**62**:125–134.
51. Weiner JM, Abramson MJ, Puy RM. Intranasal corticosteroids versus H_1-receptor antagonists in allergic rhinitis: systematic review of randomised controlled trials. BMJ 1998;**317**:1624–1629.

Exhibit G

WISCONSIN | Information Retrieval For Business and Industry

TECH SEARCH

WTS Number: 698304

Request Date: 7/20/11 9:17 AM

Conf Number: 220698

Requester: Timothy Jones
Sterne Kessler Goldstein & Fox
1100 New York Avenue, NW, Suite 900

Washington, DC 20005

RUSH

Company Phone: 202-371-2600

Requester Phone: 202-772-8789

Fax: 202-371-2540

Requester Email: Tjones@skgf.com

Send-To Email: Tjones@skgf.com

Reference: 2286.0880000

Delivery: Email

Instructions:

1.Nielsen LP;Mygind N-Drugs 61(11):pgs.1563-79,2001

Med/Q70879

An outreach service of the Kurt F. Wendt Library, University of Wisconsin - Madison
Email: wts@engr.wisc.edu | Web: http://www.wisc.edu/techsearch | Phone: (608) 262-5917

0012-6667

Requester assumes responsibility for copyright compliance.

Refer Off Campus

Drugs™

2001, Vol. 61, No. 11 (pp. 1535-1691)
ISSN: 0012-6667

Adis Drug Evaluations
Repaglinide
Insulin Glargine
Interferon Alfacon-1

Current Opinion
Long Term Inhaled Corticosteroids in COPD

Leading Articles
Treatment of Gastric Cancer
Drug Delivery Systems for Antiemetics

Review Article
Corticosteroids *vs* Antihistamines in Allergic Rhinitis

Therapy in Practice
Management of Scalp Psoriasis
Optimising Outcomes in Acute Pancreatitis

1971-2001

30

Your definitive guide to optimising drug therapy for 30 years

Available Online

adis
INTERNATIONAL
A Wolters Kluwer Company

AUCKLAND • BARCELONA • BUENOS AIRES • CHESTER • HONG KONG • MADRID
MILAN • MUNICH • OSAKA • PARIS • PHILADELPHIA • SÃO PAULO • SYDNEY

adis INTERNATIONAL
A Wolters Kluwer Company

Drugs™

Aim and Scope: *Drugs* promotes optimum pharmacotherapy by providing a programme of review articles covering the most important aspects of clinical pharmacology and therapeutics.

The Journal includes:

- Leading/current opinion articles providing an overview of contentious or emerging issues
- Definitive reviews of drugs and drug classes and their place in disease management
- Therapy in Practice articles including recommendations for specific clinical situations
- Adis Drug Evaluations reviewing the properties and place in therapy of both newer and established drugs
- Adis New Drug Profiles with expert commentary.

All manuscripts are subject to peer review by international experts. Letters to the editor are welcomed and will be considered for publication.

Editor: Dene C. Peters

Publication Manager: Rebecca Vuetilovoni

Editorial Office and Inquiries: Adis International Ltd, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, Auckland 10, New Zealand. Information on the preparation of manuscripts will be provided to authors.

E-mail: drugs@adis.co.nz http://www.adis.com

Drugs (ISSN 0012-6667) is published by Adis International Limited. Annual 2001 subscription price: $US1995; Japan ¥332 478. Annual subscription consists of 1 volume with 15 issues. Online only available for the same price as print subscription; print and online available for an additional 20%. (Further subscription information is given at the back of each issue.)

REVIEW ARTICLE

Drugs 2001; 61 (11): 1563-1579
0012-6667/01/0011-1563/$27.50/0

Intranasal Corticosteroids for Allergic Rhinitis

Superior Relief?

Lars Peter Nielsen,[1,2] *Niels Mygind*[2] and *Ronald Dahl*[2]

1 Department of Clinical Pharmacology, University of Aarhus, Aarhus, Denmark
2 Department of Respiratory Diseases, Aarhus University Hospital, Aarhus, Denmark

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 difference 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 second 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.

References

1. International Rhinitis Management Working Group. International consensus report on the diagnosis and management of rhinitis. Allergy 1994; 49: 5-34
2. Sibbald B, Rink E, D'Souza M. Is the prevalence of atopy increasing? Br J Gen Pract 1990; 40: 338-40
3. Aberg N, Sundell J, Eriksson B, et al. Prevalence of allergic diseases in school children in relation to family history, upper respiratory tract infections and residential characteristics. Allergy 1996; 5 1: 232-7
4. Bousquet J, Bullinger M, Fayol C, et al. Assessment of the quality of life in patients with perennial allergic rhinitis with the French version of the SF-36 Health Status Questionnairre. J Allergy Clin Immunol 1994; 94: 182-8
5. Juniper EF, Guyatt GH, Dolovich J. Assessment of quality of life in adolescents with allergic rhinoconjunctivitis: development and testing of a questionnaire for clinical trials. J Allergy Clin Immunol 1994 Feb; 93: 413-23

6. Simons FE. Learning impairment and allergic rhinitis. Allergy Asthma Proc 1996 Jul; 17: 185-9
7. Spector SL. Overview of comorbid associations of allergic rhinitis. J Allergy Clin Immunol 1997 Feb; 99: S773-S80
8. Mygind N. Local effect of intranasal beclomethasone dipropionate aerosol in hay fever. BMJ 1973 Nov 24; 4: 464-6
9. Holmberg K, Pipkorn U, Bake B, et al. Effects of topical treatment with H1 and H2 antagonists on clinical symptoms and nasal vascular reactions in patients with allergic rhinitis. Allergy 1989 May; 44: 281-7
10. Wang D, Clement P, Smitz J. Effect of H1 and H2 antagonists on nasal symptoms and mediator release in atopic patients after nasal allergen challenge during the pollen season. Acta Otolaryngol 1996 Jan; 116: 91-6
11. Andersson M, Nolte H, Baumgarten C, et al. Suppressive effect of loratadine on allergen-induced histamine release in the nose. Allergy 1991 Oct; 46: 540-6
12. Bousquet J, Lebel B, Chanal I, et al. Antiallergic activity of H1-receptor antagonists assessed by nasal challenge. J Allergy Clin Immunol 1988 Nov; 82: 881-7
13. Campbell A, Michel FB, Bremard-Oury C, et al. Overview of allergic mechanisms. Ebastine has more than an antihistamine effect. Drugs 1996; 52 Suppl. 1: 15-9
14. Ciprandi G, Pronzato C, Ricca V, et al. Terfenadine exerts antiallergic activity reducing ICAM- 1 expression on nasal epithelial cells in patients with pollen allergy. Clin Exp Allergy 1995 Sep; 25: 871-8
15. Ciprandi G, Buscaglia S, Pesce G, et al. Cetirizine reduces inflammatory cell recruitment and ICAM- 1 (or CD54) expression on conjunctival epithelium in both early- and late-phase reactions after allergen-specific challenge. J Allergy Clin Immunol 1995 Feb; 95: 612-21
16. Ciprandi G, Pronzato C, Ricca V, et al. Loratadine treatment of rhinitis due to pollen allergy reduces epithelial ICAM-1 expression. Clin Exp Allergy 1997 Oct; 27: 1175-83
17. Fade R, Herpin-Richard N, Rihoux JP, et al. Inhibitory effect of cetirizine 211C1 on eosinophil migration in vivo. Clin Allergy 1987 Jul; 17: 373-9
18. Naclerio RM, Kagey-Sobotka A, Lichtenstein LM, et al. Terfenadine, an H 1 antihistamine, inhibits histamine release in vivo in the human. Am Rev Respir Dis 1990 Jul; 142: 167-71
19. Jacobi HH, Skov PS, Poulsen LK, et al. Histamine and tryptase in nasal lavage fluid after allergen challenge: effect of 1 week of pretreatment with intranasal azelastine or systemic cetirizine. J Allergy Clin Immunol 1999; I03: 768-72
20. Bronsky EA, Dockhom RJ, Meltzer EO, et al. Fluticasone propionate aqueous nasal spray compared with terfenadine tablets in the treatment of seasonal allergic rhinitis. J Allergy Clin Immunol 1996 Apr; 97: 915-21
21. Klementsson H, Andersson M, Pipkorn U. Allergen-induced increase in nonspecific nasal reactivity is blocked by antihistamines without a clear-cut relationship to eosinophil influx. J Allergy Clin Inimunol 1990 Oct; 86: 466-72
22. Roquet A, Rand J, Hallden G, et al. Effect of loratadine on anti-IgE induced inflammation, histamine release and leucocyte recruitment in skin of atopics. Allergy 1995; 50: 414-20
23. Bentley AM, Walker S, Hanotte F, et al. A comparison of the effects of oral cetirizine and inhaled beclomethasone on early and late asthmatic responses to allergen and the associated increase in airways hyperresponsiveness. Clin Exp Allergy 1996; 26: 909-17
24. Brogden RN, McTavish D. Acrivastine: a review of its pharmacological properties and therapeutic efficacy in allergic rhinitis, urticaria and related disorders. Drugs 1991 Jun; 41: 927-40
25. Campoli-Richards DM, Buckley MM, Fitton A. Cetirizine. A review of its pharmacological properties and clinical potential in allergic rhinitis, pollen-induced asthma, and chronic urticaria. Drugs 1990 Nov; 40: 762-81
26. Leynadier F, Bousquet J, Murrieta M, et al. Efficacy and safety of mizolastine in seasonal allergic rhinitis. The Rhinase Study Group. Ann Allergy Asthma Immunol 1996 Feb; 76: 163-8
27. Pelaez A. Clinical efficacy of ebastine in the treatment and prevention of seasonal allergic rhinitis. Drugs 1996; 52 Suppl. 1: 35-8
28. Richards DM, Brogden RN, Heel RC, et al. Asten-fizole: a review of its pharmacodynamic properties and therapeutic efficacy. Drugs 1984 Jul; 28: 38-61
29. Simpson K, Jarvis B. Fexofenadine: a review of its use in the management of seasonal allergic rhinitis and chronic idiopathic urticaria. Drugs 2000 Feb; 59 (2): 301-21
30. Sorkin EM, Heel RC. Terfenadine: a review of its pharmacodynamic properties and therapeutic efficacy. Drugs 1985 Jan; 29: 34-56
31. Haria M, Fitton A, Peters DH. Loratadine: a reappraisal of its pharmacological properties and therapeutic use in allergic disorders. Drugs 1994; 48: 617-37
32. Ciprandi G, Ricca V, Tosca M, et al. Continous antihistamine treatment controls allergic inflammation and reduces respiratory morbidity in children with mite allergy. Allergy 1999; 54: 358-65
33. ETAC-study-group. Allergic factors associated with the development of asthma and the influence of cetirizine in a double-blind, randomized, placebo-controlled trial: first results of ETAC. Pediatr Allergy Immunol 1998; 9: 116-24
34. Simons FE, Simons M. The pharmacology and use of H 1 -receptor-antagonist drugs. N Engl J Med 1994; 330: 1663-70
35. Renwick AG. The metabolism of antihistamines and drug interactions: the role of cytochrome P450 enzymes. Clin Exp Allergy 1999; 3: 116-24
36. Simons FE, Kesselman MS, Giddins NG, et al. Asternizole-induced torsade de pointes. Lancet 1988 Sep 10; II: 624
37. Barbey JT, Anderson M, Ciprandi G, et al. Cardiovascular safety of second-generation antihistamines. Am J Rhinol 1999; 13: 23 5-43
38. Crane JK, Shih HT. Syncope and cardiac arrhythmia due to an interaction between itraconazole and terfenadine. Am J Med 1993; 95: 445-6
39. Rankin AC. Non-sedating antihistamines and cardiac arrhythmia. Lancet 1997 Oct 18; 350: 1115-6
40. Woosley RL, Sale M. QT interval: a measure of drug action. Am J Cardiol 1993; 72: 36B43B
41. van Cauwenberge P, Bachert C, Passalacqua G, et al. Consensus statement on the treatment of allergic rhinitis. European Academy of Allergology and Clinical Immunology. Allergy 2000 Feb; 55 (2): 116 -34
42. Chervinsky P, Georgitis J, Banov C, et al. Once daily loratadine versus astemizole once daily. Ann Allergy 1994 Aug; 73: 109-13
43. Wilil JA, Petersen BN, Petersen LN, et al. Effect of the non-sedative H I -receptor antagonist astemizole in perennial allergic and nonallergic rhinitis. J Allergy Clin Immunol 1985 Jun; 75: 720-7
44. Raemakers JG, O'Hanlon JF. Acrivastine, terfenadine and diphenhydramine effects on driving performance as a function of dose and time after dosing. Eur J Clin Pharmacol 1994; 47: 261-6

45. Falliers CJ, Brandon ML, Buchman E, et al. Double-blind comparison of cetirizine and placebo in the treatment of seasonal rhinitis. Ann Allergy 1991 Mar; 66: 257-62
46. McNeely W, Wiseman LR. Intranasal azelastine. A review of its efficacy in the management of allergic rhinitis. Drugs 1998 Jul; 56: 91-114
47. Noble S, McTavish D. Levocabastine. An update of its pharmacology, clinical efficacy and tolerability in the topical treatment of allergic rhinitis and conjunctivitis. Drugs 1995 Dec; 50: 1032-49
48. Rombaut N, Bliatti JZ, Curran S, et al. Effects of topical administration of levocabastine on psychomotor and cognitive function. Ann Allergy 1991; 67: 75-9
49. Wang D, Clement P, Smitz J, et al. Ihe activity of recent antiallergic drugs in the treatment of seasonal allergic rhinitis. Acta Otorhinolaryngol Belg 1996; 50: 25-32
50. Day JH, Briscoe MP, Clark RH, et al. Onset of action and efficacy of terfenadine, astemizole, cetirizine, and loratadine for the relief of symptoms of allergic rhinitis. Ann Allergy Asthma Immunol 1997 Aug; 79: 163-72
51. Frossard N, Lacronique J, Melac M, et al. Onset of action in the nasal antihistaminic effect of cetirizine and loratadine in patients with allergic rhinitis. Allergy 1997 Feb; 52: 205-9
52. Meltzer EO, Weiler JM, Widlitz MD. Comparative outdoor study of the efficacy, onset and duration of action, and safety of cetirizine, loratadine, and placebo for seasonal allergic rhinitis. J Allergy Clin Immunol 1996 Feb; 97: 617-26
53. Frossard N, Benabdesselam 0, Melac M, et al. Nasal effect of cetirizine and loratadine at 24 hours in patients with allergic rhinitis. Am J Ther 1998 Sep; 5: 307-11
54. Terrien MH, Rahm F, Fellrath JM, et al. Comparison of the effects of terfenadine with fexofenadine on nasal provocation tests with allergen. J Allergy Clin Immunol 1999 Jun; 103: 1025-30
55. al-Muhaimeed H. A parallel-group comparison of astemizole and loratadine for the treatment of perennial allergic rhinitis. J Int Med Res 1997 Jul; 25: 175-81
56. Lobaton P, Moreno F, Coulie P. Comparison of cetirizine with astemizole in the treatment of perennial allergic rhinitis and study of the concomitant effect on histamine and allergen-induced wheal responses. Ann Allergy 1990 Nov; 65: 401-5
57. Murris-Espin M, Melac M, Charpentier JC, et al. Comparison of efficacy and safety of cetirizine and ebastine in patients with perennial allergic rhinitis. Ann Allergy Asthma Immunol 1998 May; 80: 399-403
58. Renton P, Fidler C, Rosenberg R. Multicenter, crossover study of the efficacy and tolerability of terfenadine, 120 mg, versus cetirizine, 10 mg, in perennial allergic rhinitis. Ann Allergy 1991 Oct: 416-20
59. Bellioni P, Catalano B, Cervellera G, et al. Comparison of mizolastine with loratadine in the treatment of perennial allergic rhinitis. Rhinology 1996 Jun; 34: 101-4
60. Carlsen KH, Kramer J, Fagertun HE, et al. Loratadine and terfenadine in perennial allergic rhinitis. Treatment of nonresponders to the one drug with the other drug. Allergy 1993 Aug; 48: 431-6
61. Day JH, Briscoe M, Widlitz MD. Cetirizine, loratadine, or placebo in subjects with seasonal allergic rhinitis: effects after controlled ragweed pollen challenge in an environmental exposure unit. J Allergy Clin Immunol 1998 May; 10 1: 63 8-45
62. Persi L, Demoly P, Harris AG, et al. Comparison between nasal provocation tests and skin tests in patients treated with loratadine and cetirizine. J Allergy Clin Immunol 1999 Apr; 103: 591-4
63. Gervais P, Bruttinan G, Pedrali P, et al. French multicentre double-blind study to evaluate the efficacy and safety of acrivastine as compared with terfenadine in seasonal allergic rhinitis. J Int Med Res 1989; 17 Suppl. 2: 47B-53B
64. Harcup JW, Hawkes G, Saul PA. The efficacy and sedative profile of astemizole and cetirizine in the treatment of grass pollen hayfever in general practice. Br J Clin Pract 1993 May; 47: 131-5
65. Bonifazi F, Provinciali L, Antonicelli L, et al. Comparative study of terfenadine and cetirizine in hay fever: assessment of efficacy and central nervous system effects. J Investig Allergol Clin Immunol 1995 Jan; 5: 40-6
66. Caiaffa MF, ludice A, Macchia L, et al. Multicenter double-blind comparative study of terfenadine and cetirizine in hay fever. J Invest Allergol Clin Immunol 1992 May; 2: 162-6
67. Gehanno P, Bremard-Oury C, Zeisser P. Comparison of ebastine to cetirizine in seasonal allergic rhinitis in adults. Ann Allergy Asthma Immunol 1996 Jun; 76: 507-12
68. Howarth PH, Stem NIA, Roi L, et al. Double-blind, placebo-controlled study comparing the efficacy and safety of fexofenadine hydrochloride (120 and 180 ing once daily) and cetirizine in seasonal allergic rhinitis. J Allergy Clin Immunol 1999 Nov; 104: 927-33
69. Sabbah A, Daele J, Wade AG, et al. Comparison of the efficacy, safety, and onset of action of niizolastine, cetirizine, and placebo in the management of seasonal allergic rhinoconjunctivitis. MIZOCET Study Group. Ann Allergy Asthma Immunol 1999 Oct; 83: 319-25
70. Olsen OT, Nuchel PL, Hoi L, et al. Comparison of loratadine and terfenadine in allergic seasonal rhinoconjunctivitis with emphasis on nasal stuffiness and peak flow. Arzneimittelforschung 1992 Oct; 42: 1227-31
71. Berkowitz RB, Dockhom R, Lockey P, et al. Comparison of efficacy, safety, and skin test inhibition of cetirizine and astenlizole. Ann Allergy Asthma Immunol 1996 Apr; 76: 363-8
72. Cohen B, Gehanno P. Comparison of the efficacy of ebastine 10ing and 20ing once daily with that of cetirizine 10ing once daily in adults with seasonal allergic rhinitis: a multicentre double-blind study. Drugs 1996; 52 Suppl. 1: 26-9: 26-9
73. Lockey RF, Widlitz MD, Mitchell DQ, et al. Comparative study of cetirizine and terfenadine versus placebo in the symptomatic management of seasonal allergic rhinitis. Ann Allergy Asthma Immunol 1996 May; 76: 448-54
74. Baroody FM, Lim MC, Proud D, et al. Effects of loratadine and terfenadine on the induced nasal allergic reaction. Arch Otolaryngol Head Neck Surg 1996 Mar; 122: 309-16
75. Boner AL, Richelli C, Castellani C, et al. Comparison of the effects of loratadine and astemizole in the treatment of children with seasonal allergic rhinoconjunctivitis. Allergy 1992 Apr; 47: 98-102
76. Sienra-Monge JJ, Gazca-Aguilar A, Del Rio-Navarro B. Double-blind comparison of cetirizine and loratadine in children ages 2 to 6 years with perennial allergic rhinitis. Am J'ffier 1999 May; 6: 149-55
77. Charpin D, Godard P, Garay RP, et al. A multicenter clinical study of the efficacy and tolerability of azelastine nasal spray in the treatment of seasonal allergic rhinitis: a comparison with oral cetirizine. Eur Arch Otorhinolaryngol 1995; 252: 455-8
78. Passali D, Piragine F. A comparison of azelastine nasal spray and cefirizine tablets in the treatment of allergic rhinitis. J Int Med Res 1994 Jan; 22: 17-23

79. Conde HD, Palma AJ, Delgado RJ. Comparison of azelastine nasal spray and oral ebastine in treating seasonal allergic rhinitis. Curr Med Res Opin 1995; 13: 299-304
80. Gambardella R. A comparison of the efficacy of azelastine nasal spray and loratidine tablets in the treatment of seasonal allergic rhinitis. J Int Med Res 1993 Sep; 21: 268-75
81. Gastpar H, Nolte D, Aurich R, et al. Comparative efficacy of azelastine nasal spray and terfenadine in seasonal and perennial rhinitis. Allergy 1994 Mar; 49: 152-8
82. Bahmer FA, Ruprecht KW. Safety and efficacy of topical levocabastine compared with oral terfenadine. Ann Allergy 1994 May; 72: 429-34
83. Sohoel P, Freng BA, Kramer J, et al. Topical levocabastine compared with orally administered terfenadine for the prophylaxis and treatment of seasonal rhinoconjunctivitis. J Allergy Clin Immunol 1993 Jul; 92: 73-81
84. The Livostin Study Group. A comparison of topical levocabastine and oral terfenadine in the treatment of allergic rhinoconjunctivitis. Allergy 1993 Oct; 48: 530-4
85. Swedish GP Allergy Team. Topical levocabastine compared with oral loratadine for the treatment of seasonal allergic rhinoconjunctivitis. Allergy 1994 Sep; 49: 611-5
86. Mygind N, Lund V. Topical corticosteroid therapy of rhinitis. Clin Immunother 1996; 5: 122-36
87. Beato M. Gene regulation by steroid hormones. Cell 1989; 56: 335-44
88. Cato AC, Wade E. Molecular mechanisms of antfinflammatory action of glucocorticoids. Bioessays 1996; 18: 371-8
89. Godthelp T, Holm AF, Blom H, et al. The effect of fluticasone propionate aqueous nasal spray on nasal mucosal inflammation in perennial allergic rhinitis. Allergy 1995; 50: 21-4
90. Holm AF, Fokkens WJ, Godthelp T, et al. Effect of 3 months' nasal steroid therapy on nasal T cells and Langerhans cells in patients suffering from allergic rhinitis. Allergy 1995 Mar; 50: 204-9
91. Holt PG, Thomas JA. Steroids inhibit uptake and/or processing but not presentation of antigen by airway dendritic cells. Immunology 1997; 91: 145-50
92. Gomez E, Clague JE, Gatland D, et al. Effect of topical corticosteroids on seasonally induced increases in nasal mast cells. BMJ 1988 Jun 4; 296: 1572-3
93. Pipkorn U, Enerback L. Nasal mucosal mast cells and histamine in hay fever. Effect of topical glucocorticoid treatment. Int Arch Allergy Appl Immunol 1987; 84: 123-8
94. Bascom R, Wachs M, Naclerio R, et al. Basophil influx occurs after nasal antigen challenge: effects of topical corticosteroid pretreatment. J Allergy Clin Immunol 1988; 81: 580-9
95. Pipkorn U, Proud D, Lichtenstein LM, et al. Inhibition of mediator release in allergic rhinitis by pretreatment with topical glucocorticosteroids. N Engl J Med 1987 Jun 1 1; 316: 1506-10
96. Nielsen LP, Bjerke T, Christensen NW, et al. Eosinophil markers in seasonal allergic rhinitis. Intranasal fluticasone propionate inhibits local and systemic increases during the pollen season. Allergy 1998 Aug; 53: 778-85
97. Schleimer RP, Bochner BS. The effects of glucocorticoids on human eosinophils. J Allergy Clin Immunol 1994; 94: 1202-13
98. Rolfe FG, Hughes JM, Armour CL, et al. Inhibition of interleukin-5 gene expression by dexamethasone. Immunology 1992; 77: 494-9
99. Robinson D, Hamid Q, Ying S, et al. Prednisolone treatment in asthma is associated with modulation of bronchoalveolar lavage cell interleukin-4, interleukin-5 and interferon-gamma cytokine gene expression. Am Rev Respir Dis 1993; 148: 401-6
100. Weido AJ, Reece LM, Alam R, et al. Intranasal fluticasone propionate inhibits recovery of chemokines and other cytokines in nasal secretions in allergen-induced rhinitis. Ann Allergy Asthma Immunol 1996 Nov; 77: 407-15
101. Rak S, Jacobson MR, Sudderick RM, et al. Influence of prolonged treatment with topical corticosteroid (fluticasone propionate) on early and late phase nasal responses and cellular infiltration in the nasal mucosa after allergen challenge. Clin Exp Allergy 1994 Oct; 24: 930-9
102. Naclerio RM, Adkinson NFJ, Creticos PS, et al. Intranasal steroids inhibit seasonal increases in ragweedspecific immunoglobulin E antibodies. J Allergy Clin Immunol 1993 Nov; 92: 717-21
103. Pullerits T, Praks L, Sjostrand M, et al. An intranasal glucocorticoid inhibits the increase of specific IgE initiated during birch pollen season. J Allergy Clin Immunol 1997 Nov; 100: 601-5
104. Edwards TB. Effectiveness and safety of beclomethasone dipropionate, an intranasal corticosteroid, in the treatment of patients with allergic rhinitis. Clin Ther 1995 Nov; 17: 1032-41
105. Brogden RN, McTavish D. Budesonide. An updated review of its pharmacological properties, and therapeutic efficacy in asthma and rhinitis. Drugs 1992; 44: 375-407
106. Pakes GE, Brogden RN, Heel RD, et al. Flunisolide: a review of its pharmacological properties and therapeutic efficacy in rhinitis. Drugs 1980 Jun; 19: 397-411
107. Wiseman LR, Benfield P. Intranasal fluticasone propionate. A reappraisal of its pharmacology and clinical efficacy in the treatment of rhinitis. Drugs 1997; 53: 885-907
108. Onrust SV, Lamb HM. Mometasone furoate. A review of its intranasal use in allergic rhinitis. Drugs 1998 Oct; 56: 725-45
109. Jeal W, Faulds D. Trianicinolone acetonide. A review of its pharmacological properties and therapeutic efficacy in the management of allergic rhinifis. Drugs 1997 Feb; 53: 257-80
110. Aubier M, Levy J, Clerici C, et al. Different effects of nasal and bronchial glucocorticosteroid administration on bronchial hyperresponsiveness in patients with allergic rhinitis. Am Rev Respir Dis 1992 Jul; 146: 122-6
111. Corren J, Adinoff AD, Buchmeier AD, et al. Nasal beclomethasone prevents the seasonal increase in bronchial responsiveness in patients with allergic rhinitis and asthma. J Allergy Clin Immunol 1992 Aug; 90: 250-6
112. Foresi A, Pelucchi A, Gherson G, et al. Once daily intranasal fluticasone propionate (200 micrograms) reduces nasal symptoms and inflammation but also attenuates the increase in bronchial responsiveness during the pollen season in allergic rhinitis. J Allergy Clin Immunol 1996 Aug; 98: 274-82
113. Reed CE, Marcoux JP, Welsh PW. Effects of topical nasal treatment on asthma symptoms. J Allergy Clin Immunol 1988 May; 81: 1042-7
114. Wood RA, Eggleston PA. The effects of intranasal steroids on nasal and pulmonary responses to cat exposure. Am J Respir Crit Care Med 1995 Feb; 151: 315-20
115. Henriksen J, Wenzel A. Effects of intranasally adn-finistered corticosteroid (budesonide) on nasal obstruction, mouth breathing and asthma. Am Rev Respir Dis 1984; 130: 1014-8
116. Berkowitz RB, Bemstein DI, LaForce C, et al. Onset of action of mometasone faroate nasal spray (NASONEX) in seasonal allergic rhinitis. Allergy 1999 Jan; 54: 64-9
117. Lumry WR. A review of the preclinical and clinical data of newer intranasal steroids used in the treatment of allergic rhinitis. J Allergy Clin Immunol 1999 Oct; 104 (4 Pt 1): S150-8

118. Selner JC, Weber RW, Richmond GW, et al. Onset of action of aqueous beclomethasone dipropionate nasal spray in seasonal allergic rhinitis. Clin Ther 1995 Nov; 17: 1099-109
119. Day JH, Briscoe MP, Rafeiro E, et al. Onset of action of intranasal budesonide (Rhinocort aqua) in seasonal allergic rhinitis studied in a controlled exposure model. J Allergy Clin Immunol 2000 Mar; 105 (3): 489-94
120. Holm AF, Fokkens WJ, Godthelp T, et al. A1-year placebo-controlled study of intranasal fluticasone propionate aqueous nasal spray in patients with perennial allergic rhinitis: a safety and biopsy study. Clin Otolaryngol 1998 Feb; 23: 69-73
121. Banov CH, Woeffier TB, LaForce CF, et al. Once daily intranasal fluticasone propionate is effective for perennial allergic rhinitis. Ann Allergy 1994 Sep; 73: 240-6
122. Bliatia M, Campbell LM, Ross JR, et al. Intranasal budesonide once daily in seasonal allergic rhinitis. Curr Med Res Opin 199 1; 12: 287-95
123. Drouin M, Yang WH, Bertrand B, et al. Once daily mometasone furoate aqueous nasal spray is as effective as twice daily beclomethasone dipropionate for treating perennial allergic rhinitis patients. Ann Allergy Asthma Immunol 1996 Aug; 77: 15 3-60
124. Munch E, Gomez G, Harris C, et al. An open comparison of dosage frequencies of beclomethasone dipropionate in seasonal allergic rhinitis. Clin Allergy 1981 May; 11: 303-9
125. Nathan RA, Bronsky EA, Fireman P, et al. Once daily fluticasone propionate aqueous nasal spray is an effective treatment for seasonal allergic rhinitis. Ann Allergy 1991 Sep; 67: 332-8
126. Dolovich J, O'Connor M, Stepner N, et al. Double-blind comparison of intranasal fluticasone propionate, 200 micrograms, once daily with 200 micrograms twice daily in the treatment of patients with severe seasonal allergic rhinitis to ragweed. Ann Allergy 1994 May; 72: 435-40
127. Toft A, Wihl JA, Toxman J, et al. Double-blind comparison between beclomethasone dipropionate as aerosol and as powder in patients with nasal polyposis. Clin Allergy 1982 Jul; 12: 391-401
128. Andersson M, Berglund R, Greiff L, et al. A comparison of budesonide nasal dry powder with fluticasone propionate aqueous nasal spray in patients with perennial allergic rhinitis. Rhinology 1995 Mar; 33: 18-21
129. LaForee C. Use of nasal steroids in managing allergic rhinitis. J Allergy Clin Immunol 1999 Mar; 103: S388-S94
130. Cervin A, Andersson M. Intranasal steroids and septum perforation - an overlooked complication? A description of the course of events and a discussion of the causes. Rhinology 1998 Sep; 36: 12832
131. Soderberg-Warner ML. Nasal septal perforation associated with topical corticosteroid therapy. J Pediatr 1984 Nov; 105: 840-1
132. Pipkorn U, Pukander J, Suonpaa J, et al. Long-term safety of budesonide nasal aerosol: a 5.5-year follow-up study. Clin Allergy 1988 May; 18: 253-9
133. Brown HM, Storey G, Jackson FA. Beclomethasone dipropionate aerosol in treatment of perennial and seasonal rhinitis: a review of five years' experience. Br J Clin Pharmacol 1977; 4: 283-6
134. Holm AF, Godthelp T, Fokkens WJ, et al. Long-term effects of corticosteroid nasal spray on nasal inflammatory cells in patients with perennial allergic rhinitis. Clin Exp Allergy 1999 Oct; 29: 1356-66
135. Howland WC. Fluticasone propionate: topical or systemic effects? Clin Exp Allergy 1996 May; Suppl. 3: 18-22
136. Vargas R, Dockhom RJ, Findlay SR, et al. Effect of fluticasone propionate aqueous nasal spray versus oral prednisone on the hypothalamic-pituitary-adrenal axis. J Allergy Clin Immunol 1998 Aug; 102: 191-7
137. Wilson AM, Sims W, McFarlane LC, et al. Effects of intranasal corticosteroids, on adrenal, bone, and blood markers of systemic activity in allergic rhinitis. J Allergy Clin Immunol 1998 Oct; 102: 598-604
138. Wolthers OD, Pedersen S. Knemometric assessment of systemic activity of once daily intranasal drypowder budesonide in children. Allergy 1994 Feb; 49: 96-9
139. Skoner D, Rachelefsky G, Meltzer E, et al. Detection of growth suppression in children during treatment with intranasal beclomethasone dipropionate. Pediatrics 2000; 105: e23
140. Agertoft L, Pedersen S. Short-term lower leg growth rate in children with rhinitis treated with intranasal mometasone furoate and budesonide. J Allergy Clin Immunol 1999 Nov; 104: 948-52
141. Passalacqua G, Albano M, Canonica GW, et al. Inhaled and nasal corticosteroids: safety aspects. Allergy 2000; 55: 16-33
142. Scadding GK, Lund VJ, Jacques LA, et al. A placebo-controlled study of fluticasone propionate aqueous nasal spray and beclomethasone dipropionate in perennial rhinitis: efficacy in allergic and nonallergic perennial rhinitis. Clin Exp Allergy 1995 Aug; 25: 737-43
143. van As A, Bronsky EA, Dockhom RJ, et al. Once daily fluticasone propionate is as effective for perennial allergic rhinitis as twice daily beclomethasone diproprionate. J Allergy Clin Inirminol 1993 Jun; 91: 1146-54
144. Mandl M, Nolop K, Lutsky BN. Comparison of once daily mometasone furoate (Nasonex) and fluticasone propionate aqueous nasal sprays for the treatment of perennial rhinitis. 194-79 Study Group. Ann Allergy Asthma Immunol 1997 Oct; 79: 370-8
145. Haye R, Gomez EG. A multicentre study to assess long-term use of fluticasone propionate aqueous nasal spray in comparison with beclomethasone dipropionate aqueous nasal spray in the treatment of perennial rhinitis. Rhinology 1993 Dec; 31: 169-74
146. Svendsen UG, Frolund L, Madsen F, et al. Beclomethasone dipropionate versus flunisolide as topical steroid treatment in patients with perennial rhinitis. Clin Otolaryngol 1989 Oct; 14: 441-5
147. al-Mohaimeid H. A parallel-group comparison of budesonide and beclomethasone dipropionate for the treatment of perennial allergic rhinitis in adults. J Int Med Res 1993 Mar; 21: 67-77
148. Adamopoulos G, Manolopoulos L, Giotakis I. A comparison of the efficacy and patient acceptability of budesonide and beclomethasone dipropionate aqueous nasal sprays in patients with perennial rhinitis. Clin Otolaryngol 1995 Aug; 20: 340-4
149. Day J, Carrillo T. Comparison of the efficacy of budesonide and fluticasone propionate aqueous nasal spray for once daily treatment of perennial allergic rhinitis. J Allergy Clin Immunol 1998 Dec; 102: 902-8
150. McAllen MK, Portillo PR, Parr EJ, et al. Intranasal flunisolide, placebo and beclomethasone dipropionate in perennial rhinitis. Br J Dis Chest 1980 Jan; 74: 32-6
151. Sahay JN, Chatterjee SS, Engler C. A comparative trial of flunisolide and beclomethasone dipropionate in the treatment of perennial allergic rhinitis. Clin Allergy 1980 Jan; 10: 65-70
152. Graft D, Aaronson D, Chervinsky P, et al. A placebo- and active-controlled randon-tized trial of prophylactic treatment of

seasonal allergic rhinitis with mometasone furoate aqueous nasal spray. J Allergy Clin Immunol 1996 Oct; 98: 724-31

153. Hebert JP, Nolop K, Lutsky BN. Once-daily mometasone furoate aqueous nasal spray (Nasonex) in seasonal allergic rhinitis: an active- and placebo-controlled study. Allergy 1996 Aug; 51: 569-76
154. Ratner PH, Paull BR, Findlay SR, et al. Fluticasone propionate given once daily is as effective for seasonal allergic rhinitis as beclomethasone dipropionate given twice daily. J Allergy Clin Immunol 1992 Sep; 90: 285-91
155. Vanzieleghern NIA, Juniper EF. A comparison of budesonide and beclomethasone dipropionate nasal aerosols in ragweed-induced rhinitis. J Allergy Clin Immunol 1987 Jun; 79: 887-92
156. Sipila P, Sorri M, Ojala K, et al. Comparative trial of flunisolide and beclomethasone dipropionate nasal sprays inpatients with seasonal allergic rhinitis. Allergy 1983 Jul; 38: 303-7
157. Aasand G, Etholm BO, Skjostad M, et al. Flunisolide nasal spray compared to beclomethasone dipropionate in the treatment of seasonal rhinitis. Rhinology 1982 Dec; 20: 205-11
158. Langrick AF. Comparison of flunisolide and beclomethasone dipropionate in seasonal allergic rhinitis. Curr Med Res Opin 1984; 9: 290-5
159. Pipkorn U, Geterud A. A comparative trial testing budesonide and flunisolide nasal sprays in patients with seasonal allergic rhinitis. Ann Allergy 1984 Mar; 52: 183-6
160. Small P, Houle PA, Day JH, et al. A comparison of triamcinolone acetonide nasal aerosol spray and fluticasone propionate aqueous solution spray in the treatment of spring allergic rhinitis. J Allergy Clin Immunol 1997 Nov; 100: 592-5
161. Pipkorn U. Hay fever treatment with budesonide and beclomethasone dipropionate twice daily – a clinical comparison. Rhinology 1983 Dec; 21: 335-40
162. McArthur JG. A comparison of budesonide and beclomethasone dipropionate sprays in the treatment of seasonal allergic rhinitis. Clin Otolaryngol 1994 Dec; 19: 537-42
163. Stem MA, Dahl P, Nielsen LP, et al. A comparison of aqueous suspensions of budesonide nasal spray (128 micrograms and 256 micrograms once daily) and fluticasone propionate nasal spray (200 micrograms once daily) in the treatment of adult patients with seasonal allergic rhinitis. Am J Rhinol 1997 Jul; 11: 323-30
164. Robinson AC, Cherry JR, Daly S. Double-blind cross-over trial comparing beclomethasone dipropionate and terfenadine in perennial rhinitis. Clin Exp Allergy 1989 Sep; 19: 569-73
165. Bunnag Q Jareoncharsri P, Wong EC. A double-blind comparison of nasal budesonide and oral astemizole for the treatment of perennial rhinitis. Allergy 1992 Aug; 47: 313-7
166. Sibbald B, Hilton S, D'Souza M. An open cross-over trial comparing two doses of astemizole and beclomethasone dipropionate in the treatment of perennial rhinitis. Clin Allergy 1986 May; 16: 203-11
167. Davies RJ, Lund VJ, Harten-Ash VJ. The effect of intranasal azelastine and beclomethasone on the symptoms and signs of nasal allergy in patients with perennial allergic rhinitis. Rhinology 1993 Dec; 31: 159-64
168. Stern MA, Wade AG, Ridout SM, et al. Nasal budesonide offers superior symptom relief in perennial allergic rhinitis in comparison to nasal azelastine. Ann Allergy Asthma Immunol 1998 Oct; 8 1: 354-8
169. van de Heyning PH, van HJ, Creten W, et al. Effect of topical levocabastine on allergic and non-allergic perennial rhinitis. A double-blind study, levocabastine vs. placebo, followed by an open, prospective, single-blind study on beclomethasone. Allergy 1988 Jul; 43: 386-91
170. Beswick KB, Kenyon GS, Cherry JR. A comparative study of beclomethasone dipropionate aqueous nasal spray with terfenadine tablets in seasonal allergic rhinitis. Curr Med Res Opin 1985; 9: 5607
171. Lancer JM, Jones AS, Stevens JC, et al. A comparison by rhinomanometry of beclomethasone and terfenadine in the treatment of seasonal rhinitis. J Laryngol Otol 1987; 10 1: 350-4
172. Darnell R, Pecoud A, Richards DH. A double-blind comparison of fluticasone propionate aqueous nasal spray, terfenadine tablets and placebo in the treatment of patients with seasonal allergic rhinitis to grass pollen. Clin Exp Allergy 1994 Dec; 24: 1144-50
173. van Bavel J, Findlay SR, Hampel FCJ, et al. Intranasal fluticasone propionate is more effective than terfenadine tablets for seasonal allergic rhinitis. Arch Intern Med 1994 Dec 12; 154: 2699-704
174. Frolund L. Efficacy of an oral antihistamine, loratadine, as compared with a nasal steroid spray, beclomethasone dipropionate, in seasonal allergic rhinitis. Clin Otolaryngol 1991 Dec; 16: 527-31
175. Condemi J, Schulz R, Lim J. Triamcinolone acetonide aqueous nasal spray versus loratadine in seasonal allergic rhinitis: efficacy and quality of life. Ann Allergy Asthma Immunol 2000 May; 84: 533-8
176. Schoenwetter W, Lim J. Comparison of intranasal triaincinolone acetonide with oral loratadine for the treatment of patients with seasonal allergic rhinitis. Clin Ther 1995 May; 17: 479-92
177. Gehanno P, Desfougeres JL. Fluticasone propionate aqueous nasal spray compared with oral loratadine in patients with seasonal allergic rhinitis. Allergy 1997 Apr; 52: 445-50
178. Jordana G, Dolovich J, Briscoe MP, et al. Intranasal fluticasone propionate versus loratadine in the treatment of adolescent patients with seasonal allergic rhinitis. J Allergy Clin Immunol 1996 Feb; 97: 588-95
179. Salomonsson P, Gottberg L, Heilbom H, et al. Efficacy of an oral antihistamine, astemizole, as compared to a nasal steroid spray in hay fever. Allergy 1988 Apr; 43: 214-8
180. Wood SF. Oral antihistamine or nasal steroid in hay fever: a double-blind double-dummy comparative study of once daily oral astemizole vs twice daily nasal beclomethasone dipropionate. Clin Allergy 1986 May; 16: 195-201
181. Bernstein DI, Creticos PS, Busse WW, et al. Comparison of triamcinolone acetonide nasal inhaler with astemizole in the treatment of ragweed-induced allergic rhinitis. J Allergy Clin Immunol 1996 Mar; 97: 749-55
182. Vervloet D, Charpin D, Desfougeres X. Intranasal fluticasone once daily compared with once daily cetirizine in the treatment of seasonal allergic rhinitis. Clin Drug Invest 1997; 13: 291-8
183. Weiner JM, Abramson MJ, Puy RM. Intranasal corticosteroids versus oral H1 receptor antagonists in allergic rhinitis: systematic review of randomized controlled trials. BMJ 1998 Dec 12; 317: 1624-
184. Newson-Smith G, Powell M, Baelire M, et al. A placebo controlled study comparing the efficacy of intranasal azelastine and beclomethasone in the treatment of seasonal allergic rhinitis. Eur Arch Otorhinolaryngol 1997; 254: 236-41
185. Pelucchi A, Chiapparino A, Mastropasqua B, et al. Effect of intranasal azelastine and beclomethasone dipropionate on nasal symptoms, nasal cytology, and bronchial responsiveness to methacholine in allergic rhinitis in response to grass pollens. J Allergy Clin Immunol 1995 Feb; 95: 515-23

186. Dorow P, Aurich R, Petzold U. Efficacy and tolerability of azelastine nasal spray in patients with allergic rhinitis compared to placebo and budesonide. Arzneinlittelforschung 1993 Aug; 43: 909-12
187. Wang D, Smitz J, De Waele M, et al. Effect of topical applications of budesonide and azelastine on nasal symptoms, eosinophil count and mediator release in atopic patients after nasal allergen challenge during the pollen season. Int Arch Allergy Immunol 1997 Oct; 114: 185-92
188. Svensson C, Andersson M, Greiff L, et al. Effects of topical budesonide and levocabastine on nasal symptoms and plasma exudation responses in seasonal allergic rhinitis. Allergy 1998 Apr; 53: 367-74
189. Di Lorenzo G, Gervasi F, Drago A, et al. Comparison of the effects of fluticasone propionate, aqueous nasal spray and levocabastine on inflanunatory cells in nasal lavage and clinical activity during the pollen season in seasonal rhinitics. Clin Exp Allergy 1999 Oct; 29: 1367-77
190. Ortolani C, Foresi A, Di Lorenzo G, et al. A double-blind, placebo-controlled comparison of treatment with fluticasone propionate and levocabastine in patients with seasonal allergic rhinitis. FLNC02 Italian Study Group. Allergy 1999 Nov; 54: 1173-80
191. Juniper EF, Kline PA, Hargreave FE, et al. Comparison of beclomethasone dipropionate aqueous nasal spray, astemizole, and the combination in the prophylactic treatment of ragweed pollen-induced rhinoconjunctivitis. J Allergy Clin Immunol 1989 Mar; 83: 627-33
192. Ratner PH, van Bavel J, Martin BG, 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. J Fam Pract 1998 Aug; 47: 118-25
193. Simpson RJ. Budesonide and terfenadine, separately and in combination, in the treatment of hay fever. Ann Allergy 1994 Dec; 73: 497-502
194. Brooks CD, Francom SF, Peel BG, et al. Spectrum of seasonal allergic rhinitis symptom relief with topical corticoid and oral antihistamine given singly or in combination. Am J Rhinol 1996; 10: 193-9
195. Backhouse Cl, Finnamore VP, Gosden CW. Treatment of seasonal allergic rhinitis with flunisolide and terfenadine. J Int Med Res 1986; 14: 35-41
196. Juniper EF, Guyatt GH, Ferrie PJ, et al. First-line treatment of seasonal (ragweed) rhinoconjunctivitis. A randomized management trial comparing a nasal steroid spray and a nonsedating antihistamine. CMAJ 1997 Apr 15; 156: 1123-31
197. Kozma CM, Schulz RM, Sclar DA, et al. A comparison of costs and efficacy of intranasal fluticasone propionate and terfenadine tablets for seasonal allergic rhinitis. Clin Ther 1996 Mar; 18: 334-46
198. Berka C, Chin W. Fluticasone propionate intranasal steroid: cost-effectiveness vs antihistamines. J Allergy Clin Immunol 1994; 93: 165
199. Slater JW, Zechnich AD, Haxby DG. Second-generation antihistamines: a comparative review. Drugs 1999 Jan; 57: 31-47
200. Dykewicz MS, Fineman S. Executive summary of Joint Task Force Practice Parameters on Diagnosis and Management of Rhinitis. Ann Allergy Asthma Immunol 1998; 81: 463-8

Correspondence and offprints: Dr *Lars Peter Nielsen*, Department of Clinical Pharmacology, The Bartholin Building, University of Aarhus, DK-8000, Aarhus, Denmark.
E-mail: lpn@dadlnet.dk

Exhibit H

WISCONSIN | Information Retrieval For Business and Industry

TECH SEARCH

WTS Number: 698305

698305

Request Date: 7/20/11 9:17 AM

Conf Number: 220698

Requester: Timothy Jones
Sterne Kessler Goldstein & Fox
1100 New York Avenue, NW, Suite 900
Washington, DC 20005

RUSH

Company Phone: 202-371-2600

Requester Phone: 202-772-8789

Fax: 202-371-2540

Requester Email: Tjones@skgf.com

Send-To Email: Tjones@skgf.com

Reference: 2286.0880000

Delivery: Email

Instructions:

2.Salib RJ;Howarth PH-Drug Saf 26(12):pgs.863-93,2003

Med/ Q7D834

0114-5916

Requester assumes responsibility for copyright compliance.

Refer Off Campus

Drug Safety™

2003, Vol. 26, No. 12 (pp. 829-911)
ISSN: 0114-5916

Leading Articles
Pharmacovigilance of Herbal Medicines
Benefit-Risk Analysis: Proposed Quantitative Approaches

Review Article
Intranasal Antihistamines and Intranasal Corticosteroids in Allergic Rhinitis

Original Research Article
Adverse Effects of ACE Inhibitors in Heart Failure

Available Online

adis INTERNATIONAL
A Wolters Kluwer Company

AUCKLAND • BARCELONA • BUENOS AIRES • CHESTER • HONG KONG • MADRID • MILAN
MUNICH • OSAKA • PARIS • PARSIPPANY • PHILADELPHIA • ROME • SÃO PAULO • TOKYO

adis
INTERNATIONAL
A Wolters Kluwer Company

Drug Safety™

Aim and Scope: *Drug Safety* advances the rational use of pharmacotherapy by providing a programme of review articles offering guidance for safe and effective drug utilisation and prescribing.

The Journal includes:

- Leading/current opinion articles providing an overview of contentious or emerging issues
- Definitive reviews on the epidemiology, clinical features, prevention and management of adverse effects of an individual drug or drug class when given at therapeutic dosages or following overdose
- Benefit-risk assessments providing an in-depth review of adverse effects and efficacy data for a drug in a specific disease to place the benefit-risk relationship in clear perspective
- Practical reviews covering drug use in particular 'at-risk' patient groups to achieve optimal outcomes
- Concept reviews covering issues in pharmacovigilance, risk minimisation and medication error prevention
- Original research articles will also be considered for publication.

All manuscripts are subject to peer review by international experts. Letters to the editor are welcomed and will be considered for publication.

Editor: Rosie Stather

Publication Manager: June B. Hearne

Editorial Office and Inquiries: Adis International Ltd, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, Auckland 1311, New Zealand. Information on the preparation of manuscripts will be provided to authors.

E-mail: drugsafety@adis.co.nz http://www.adis.com/drugsafety

Drug Safety (ISSN 0114-5916) is published as 1 volume with 15 issues by Adis International Limited. Annual 2003 institutional subscription price: $US1725. Personal subscription rate: $US195. For 2003, all subscriptions to Adis titles will include electronic access at no extra cost. (Further subscription information is given at the back of each issue.)

REVIEW ARTICLE

Drug Safety 2003; 26 (12): 863-893
0114-5916/03/0012-0863/$30.00/0

Safety and Tolerability Profiles of Intranasal Antihistamines and Intranasal Corticosteroids in the Treatment of Allergic Rhinitis

Rami Jean Salib and *Peter Hugo Howarth*

Respiratory Cell and Molecular Biology, Faculty of Medicine, Southampton General Hospital, Southampton, United Kingdom

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

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.

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 corticosteroids, 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 symptoms, 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 differences 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

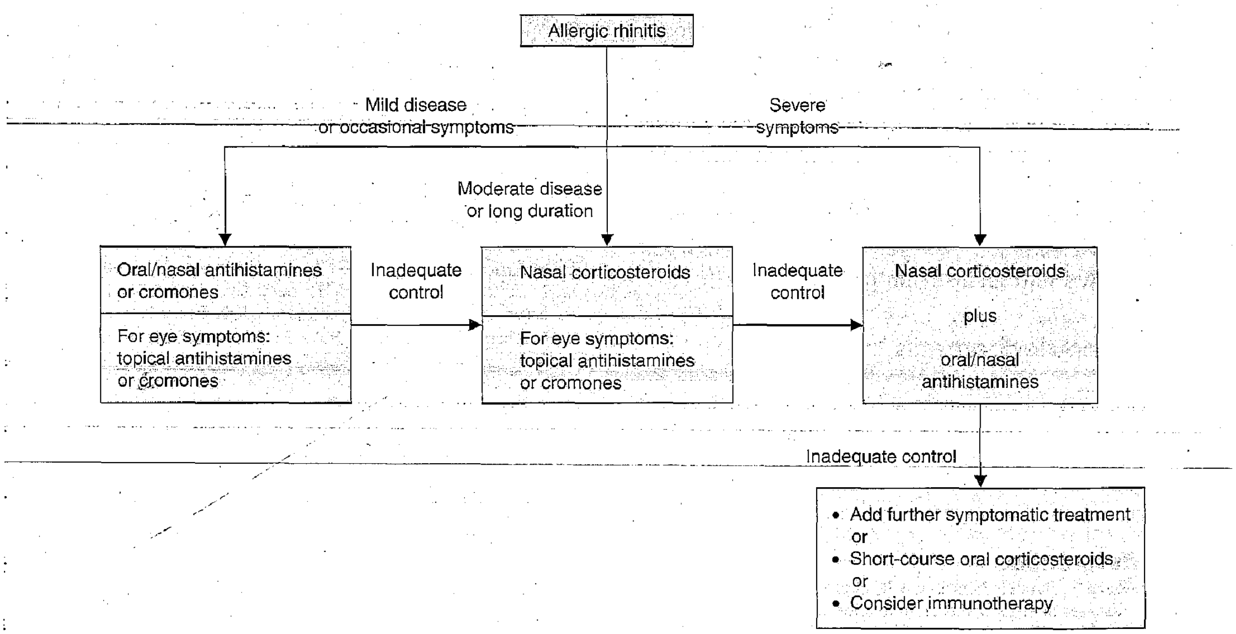


Fig. 1. Algorithm of the management protocol for allergic rhinitis based on the allergic rhinitis and its impact on asthma (ARIA) guidelines.

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]

Acknowledgements

This work was supported by a research grant from the Royal College of Surgeons of England. There are no potential conflicts of interest directly relevant to the content of this review.

References

1. Aberg N, Sundell J, Eriksson B, et al. Prevalence of allergic diseases in schoolchildren in relation to family history, upper respiratory infections, and residential characteristics. Allergy 1996; 51 (4): 232-7
2. Sibbald B. Epidemiology of allergic rhinitis. In: Burr ML, editor. Epidemiology of clinical allergy. Monographs in allergy. Basel: Karger, 1993; 31: 61-9
3. Strachan D, Sibbald B, Weiland S, et al. Worldwide variations in prevalence of symptoms of allergic rhinoconjunctivitis in children: the International Study of Asthma and Allergies in Childhood (ISAAC). Pediatr Allergy Immunol 1997; 8 (4): 161-76
4. Spector SL. Overview of comorbid associations of allergic rhinitis. J Allergy Clin Immunol 1997; 99 (2): S773-80
5. Bousquet J, Van Cauwenberge P, Khaltaev N, et al. Allergic rhinitis and its impact on asthma. J Allergy Clin Immunol 2001; 108 (5 Suppl.): S147-334
6. Staub AM, Bovet D. Action de la thymoxyethyldiethylamine (929F) et des ethers phenoliques sur le choc anaphylactique. CR Soc Biol Fil 1937; 125: 818-21
7. Levy L, Seabury JH. Spirometric evaluations of Benadryl in asthma. J Allergy 1947; 18: 244-50
8. Herxheimer H. Antihistamines in bronchial asthma. BMJ 1949; 2: 901-5
9. Pandit PR, Kulkarni SD, Joglekar GV. Study of relationship between antihistaminic, anticholinergic and central depressant properties of various antihistaminics. Indian J Med Sci 1973; 27 (12): 920-4
10. Stone CA, Wenger H, Ludden CT, et al. Antiserotonin-antihistaminic properties of cyroheptadine. J Pharmacol Exp Ther 1961; 131: 73-84
11. Byck R. Drugs and the treatment of psychiatric disorders. In: Goodman LS, Gilman A, editors. The pharmacological basis of therapeutics. New York: McMillan, 1975: 152-200
12. Casterline CL, Evans R. Further studies on the mechanism of human histamine-induced asthma: the effect of an aerosolized H1 receptor antagonist (diphenhydramine). J Allergy Clin Immunol 1977; 59 (6): 420-4
13. Moser L, Huther KJ, Koch-Weser J, et al. Effects of terfenadine and diphenhydramine alone or in combination with diazepam or alcohol on psychomotor performance and subjective feelings. Eur J Clin Pharmacol 1978; 14 (6): 417-23
14. Cheng HC, Woodward JK. Antihistaminic effect of terfenadine: a new piperidine-type-antihistamine. Drug Dev Res 1982; 2: 181-96
15. Noble S, McTavish D. Levocabastine: an update of its pharmacology, clinical efficacy and tolerability in the topical treatment of allergic rhinitis and conjunctivitis. Drugs 1995; 50 (6): 1032-49
16. Howarth PH. Antihistamines in rhinoconjunctivitis. In: Simons E, editor. Histamines and H1-antihistamines in allergic diseases. New York: Marcel Dekker Inc, 2002: 179-220
17. Holmberg K, Pipkorn U, Bake B, et al. Effects of topical treatment with H1 and H2 antagonists on clinical symptoms and nasal vascular reactions in patients with allergic rhinitis. Allergy 1989; 44 (4): 281-7
18. Palma-Carlos AG, Palma-Carlos ML, Rombaut N. The effect of levocabastine nasal spray in nasal provocation tests. Int J Clin Pharmacol Res 1988; 8 (1): 25-30
19. Corren J, Rachelefsky G, Spector S, et al. Onset and duration of action of levocabastine nasal spray in atopic patients under nasal challenge conditions. J Allergy Clin Immunol 1999; 103 (4): 574-80
20. Schata M, Jorde W, Richarz-Barthauer U. Levocabastine nasal spray better than sodium cromoglycate and placebo in the topical treatment of seasonal allergic rhinitis. J Allergy Clin Immunol 1991; 87 (4): 873-8

21. Hampel FC, Martin BG, Dolen J, et al. Efficacy and safety of levocabastine nasal spray for seasonal allergic rhinitis. Am J Rhinol 1999; 13 (1): 55-62
22. Bende M, Pipkorn U. Topical levocabastine, a selective H1 antagonist, in seasonal allergic rhinoconjunctivitis. Allergy 1987; 42 (7): 512-5
23. Søhoel P, Freng BA, Kramer J, et al. Topical levocabastine compared with orally administered terfenadine for the prophylaxis and treatment of seasonal rhinoconjunctivitis. J Allergy Clin Immunol 1993; 92 (1 Pt 1): 73-81
24. Palma-Carlos AG, Chieira C, Conde TA, et al. Double-blind comparison of levocabastine nasal spray with sodium cromoglycate nasal spray in the treatment of seasonal allergic rhinitis. Ann Allergy 1991; 67 (4): 394-8
25. Knight A. The role of levocabastine in the treatment of allergic rhinoconjunctivitis. Br J Clin Pract 1994; 48 (3): 139-43
26. Kremer B, Tundermann A, Goldschmidt O. Onset of action, effectiveness and tolerance of levocabastine and nedocromil in topical therapy of seasonal allergic rhinoconjunctivitis: The Deutsche Rhinitis-Studiengruppe. Arzneimittel Forschung 1998; 48 (9): 924-30
27. Di Lorenzo G, Gervasi F, Drago A, et al. Comparison of the effects of fluticasone propionate, aqueous nasal spray and levocabastine on inflammatory cells in nasal lavage and clinical activity during the pollen season in seasonal rhinitics. Clin Exp Allergy 1999; 29 (10): 1367-77
28. Ortolani C, Foresi A, Di Lorenzo G, et al. A double-blind, placebo-controlled comparison of treatment with fluticasone propionate and levocabastine in patients with seasonal allergic rhinitis: FLNCO2 Italian Study Group. Allergy 1999; 54 (11): 1173-80
29. Baraldi E, Azzolin NM, Carra S, et al. Effect of topical steroids on nasal nitric oxide production in children with perennial allergic rhinitis: a pilot study. Respir Med 1998; 92 (3): 558-61
30. van de Heyning PH, van Haesendonck J, Creten W, et al. Effect of topical levocabastine on allergic and non-allergic perennial rhinitis: a double-blind study, levocabastine vs placebo, followed by an open, prospective, single-blind study on beclomethasone. Allergy 1988; 43 (5): 386-91
31. International Product Information Document. Livostin Clinical Monograph, Janssen Pharmaceutica, 1995
32. Borum S, Nielsen K, Bisgaard H, et al. Experimentally induced nasal hypersecretion does not reduce the efficacy of intranasal levocabastine. Rhinology 1998; 36 (4): 153-5
33. Dechant KL, Goa KL. Levocabastine: a review of its pharmacological properties and therapeutic potential as a topical antihistamine in allergic rhinitis and conjunctivitis. Drugs 1991; 41 (2): 202-24
34. Heykants J, Van Peer A, Van de Velde V, et al. The pharmacokinetic properties of topical levocabastine: a review. Clin Pharmacokinet 1995; 29 (4): 221-30
35. Okuda M, Tomiyama S, Baba S, et al. Phase I study of R 50547 (levocabastine hydrochloride) nasal spray (1st report): single administration study [in Japanese]. Jibi To Rinsho 1995; 41 Suppl. 1: 281-300
36. Okuda M, Tomiyama S, Ohinishi M, et al. Phase I study of R 50547 (levocabastine hydrochloride) nasal spray (2nd report): repeated administration study [in Japanese]. Jibi To Rinsho 1995; 41 Suppl. 1: 301-25
37. Heykants JJP. Antihistamines. In: Van Boxel CJ, Holford NHG, Danhof M, editors. The in vivo study of drug action. Amsterdam: Elsevier Science, 1992: 337-56
38. Pesco-Koplowitz L, Hassell A, Lee P, et al. Lack of effects of erythromycin and ketoconazole on the pharmacokinetics and pharmacodynamics of steady-state intranasal levocabastine. J Clin Pharmacol 1999; 39 (1): 76-85
39. Frostad AB, Olsen AK. A comparison of topical levocabastine and sodium cromoglycate in the treatment of pollen-provoked allergic conjunctivitis. Clin Exp Allergy 1993; 23 (5): 406-9
40. Davies BH, Mullins J. Topical levocabastine is more effective than sodium cromoglycate for the prophylaxis and treatment of seasonal allergic conjunctivitis. Allergy 1993; 48 (7): 519-24
41. Vermeulen J, Mercer M. Comparison of the efficacy and tolerability of topical levocabastine and sodium cromoglycate in the treatment of seasonal allergic rhinoconjunctivitis in children. Pediatr Allergy Immunol 1994; 5 (4): 209-13
42. Howarth PH. A review of the tolerability and safety of levocabastine eye drops and nasal spray: implications for patient management. Mediators Inflamm 1995; 4 Suppl 1: S26-S30
43. Bahmer FA, Ruprecht KW. Safety and efficacy of topical levocabastine compared with oral terfenadine. Ann Allergy 1994; 72 (5): 429-34
44. A comparison of topical levocabastine and oral terfenadine in the treatment of allergic rhinoconjunctivitis: The Livostin Study Group. Allergy 1993; 48 (7): 530-4
45. Drouin MA, Yang WH, Horak F. Faster onset of action with topical levocabastine than with oral oral cetirizine. Mediators Inflamm 1995; 4 Suppl. 1: S5-S10
46. Azevedo M, Castel-Branco MG, Oliveira JF, et al. Double-blind comparison of levocabastine eye drops with sodium cromoglycate and placebo in the treatment of seasonal allergic conjunctivitis. Clin Exp Allergy 1991; 21 (6): 689-94
47. Wihl JA, Rudblad S, Kjellen H, et al. Levocabastine eye drops versus sodium cromoglycate in seasonal allergic conjunctivitis. Clin Exp Allergy 1991; 21 Suppl. 2: 37-8
48. Busse W, Janssens M, Eisen G, et al. Is there a place for topical antihistamine/decongestant combination in the treatment of seasonal allergic rhinitis? Belgium: Janssen Pharmaceutica, 1995 (Data on file)
49. Kurzawa R, Kossek M, Doniec Z, et al. Clinical efficacy and safety of levocabastine in the therapy in children suffering from seasonal allergic rhinitis and conjunctivitis who are less than 12 year of age. Pol Merkuriusz Lek 1998; 4 (23): 269-72
50. Hermens WA, Merkus FW. The influence of drugs on nasal ciliary movement. Pharm Res 1987; 4 (6): 445-9
51. Merkus FW, Schusler-van Hees MT. Influence of levocabastine suspension on ciliary beat frequency and mucociliary clearance. Allergy 1992; 47 (3): 230-3
52. Rombaut N, Bhatti JZ, Curran S, et al. Effects of topical administration of levocabastine on psychomotor and cognitive function. Ann Allergy 1991; 67 (1): 75-9
53. Arriaga F, Rombaut N. Absence of central effects with levocabastine eye drops. Allergy 1990; 45 (7):552-4
54. Mazzotta P, Loebstein R, Koren G. Treating allergic rhinitis in pregnancy: safety considerations. Drug Saf 1999; 20 (4): 361-75
55. Horak F, Stubner UP. Comparative tolerability of second generation antihistamines. Drug Saf 1999; 20 (5): 385-401
56. McNeely W, Wiseman LR. Intranasal azelastine: a review of its efficacy in the management of allergic rhinitis. Drugs 1998; 56 (1): 91-114
57. Simons FE, Simons KJ. Second-generation H1-receptor antagonists. Ann Allergy 1991; 66 (1): 5-16

58. McTavish D, Sorkin EM. Azelastine: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential. Drugs 1989; 38 (5): 778-800
59. ASTA Medica AG. Azelastine product monograph. Frankfurt am Main Germany, 1997 May
60. Ciprandi G, Pronzato C, Passalacqua G, et al. Topical azelastine reduces eosinophil activation and intercellular adhesion molecule-1 expression on nasal epithelial cells: an antiallergic activity. J Allergy Clin Immunol 1996; 98 (6 Pt 1): 1088-96
61. Ciprandi G, Ricca V, Passalacqua G, et al. Seasonal rhinitis and azelastine: long- or short-term treatment? J Allergy Clin Immunol 1997; 99 (3): 301-7
62. Pelucchi A, Chiapparino A, Mastropasqua B, et al. Effect of intranasal azelastine and beclomethasone dipropionate on nasal symptoms, nasal cytology, and bronchial responsiveness to methacholine in allergic rhinitis in response to grass pollens. J Allergy Clin Immunol 1995; 95 (2): 515-23
63. Weiler JM, Meltzer EO, Benson PM, et al. A dose-ranging study of the efficacy and safety of azelastine nasal spray in the treatment of seasonal allergic rhinitis with an acute model. J Allergy Clin Immunol 1994; 94 (6 Pt 1): 972-80
64. Ratner PH, Findlay SR, Hampel F, et al. A double-blind, controlled trial to assess the safety and efficacy of azelastine nasal spray in seasonal allergic rhinitis. J Allergy Clin Immunol 1994; 94 (5): 818-25
65. Meltzer EO, Weiler JM, Dockhorn RJ, et al. Azelastine nasal spray in the management of seasonal allergic rhinitis. Ann Allergy 1994; 72 (4): 354-9
66. LaForce C, Dockhorn RJ, Prenner BM, et al. Safety and efficacy of azelastine nasal spray (Astelin NS) for seasonal allergic rhinitis: a 4-week comparative multicenter trial. Ann Allergy Asthma Immunol 1996; 76 (2): 181-8
67. Herman D, Garay R, Le Gal M. A randomized double-blind placebo controlled study of azelastine nasal spray in children with perennial rhinitis. Int J Pediatr Otorhinolaryngol 1997; 39 (1): 1-8
68. Banov CH, Lieberman P. Efficacy of azelastine nasal spray in the treatment of vasomotor (perennial nonallergic) rhinitis. Ann Allergy Asthma Immunol 2001; 86 (1): 28-35
69. Gehanno P, Deschamps E, Garay E, et al. Vasomotor rhinitis: clinical efficacy of azelastine nasal spray in comparison with placebo. J Otorhinolaryngol Relat Spec 2001; 63 (2): 76-81
70. Berger WE, Fineman SM, Lieberman P, et al. Double-blind trials of azelastine nasal spray monotherapy versus combination therapy with loratadine tablets and beclomethasone nasal spray in patients with seasonal allergic rhinitis: Rhinitis Study Groups. Ann Allergy Asthma Immunol 1999; 82 (6): 535-41
71. Newson-Smith G, Powell M, Baehre M, et al. A placebo controlled study comparing the efficacy of intranasal azelastine and beclomethasone in the treatment of seasonal allergic rhinitis. Eur Arch Otorhinolaryngol 1997; 254 (5): 236-41
72. Davies RJ, Lund VJ, Harten-Ash VJ. The effect of intranasal azelastine and beclomethasone on the symptoms and signs of nasal allergy in patients with perennial allergic rhinitis. Rhinology 1993; 31 (4): 159-64
73. Gastpar H, Aurich R, Petzold U, et al. Intranasal treatment of perennial allergic rhinitis: comparison of azelastine nasal spray and budesonide nasal aerosol. Arzneimittel Forschung 1993; 43 (4): 475-9
74. Dorow P, Aurich R, Petzold U. Efficacy and tolerability of azelastine nasal spray in patients with allergic rhinitis compared to placebo and budesonide. Arzneimittel Forschung 1993; 43 (8): 909-12
75. Stern MA, Wade AG, Ridout SM, et al. Nasal budesonide offers superior symptom relief in perennial allergic rhinitis in comparison to nasal azelastine. Ann Allergy Asthma Immunol 1998; 81 (4): 354-8
76. Mösges R, Spaeth J, Klimek L. Efficacy and tolerability of levocabastine and azelastine nasal sprays for the treatment of allergic rhinitis. Mediators Inflamm 1995; 4 Suppl. 1: S11-5
77. Passali D, Piragine F. A comparison of azelastine nasal spray and cetirizine tablets in the treatment of allergic rhinitis. J Int Med Res 1994; 22 (1): 17-23
78. Charpin D, Godard P, Garay RP, et al. A multicenter clinical study of the efficacy and tolerability of azelastine nasal spray in the treatment of seasonal allergic rhinitis: a comparison with oral cetirizine. Eur Arch Otorhinolaryngol 1995; 252 (8): 455-8
79. Conde Hernández DJ, Palma Aqilar JL, Delgado Romero J. Comparison of azelastine nasal spray and oral ebastine in treating seasonal allergic rhinitis. Curr Med Res Opin 1995; 13 (6): 299-304
80. Gambardella R. A comparison of the efficacy of azelastine nasal spray and loratadine tablets in the treatment of seasonal allergic rhinitis. J Int Med Res 1993; 21 (5): 268-75
81. Gastpar H, Nolte D, Aurich R, et al. Comparative efficacy of azelastine nasal spray and terfenadine in seasonal and perennial rhinitis. Allergy 1994; 49 (3): 152-8
82. British National Formulary. Number 43. Published by the British Medical Association and the Pharmaceutical Society of Great Britain, 2002 Mar
83. Kisicki JC, Howard JR, Riethmuller-Winzen H, et al. Azelastine nasal spray: twenty-nine day tolerability and safety study in healthy subjects. Asta Pharma AG / Carter-Wallace Ltd. CP-90-254; 1990 Jul 2 (Data on file)
84. Weliky I, Howard JR, Wichmann JK. Absolute bioavailability (AB) and pharmacokinetics (PK) of azelastine (AZ) [abstract]. Pharmacol Res 1990; 22 Suppl. 7: S247
85. Riethmuller-Winzen H, Peter G, Buker KM, et al. Tolerability, pharmacokinetics and dose linearity of azelastine hydrochloride in healthy subjects. Arzneimittel Forschung 1994; 44 (10): 1136-40
86. Peter G, Romeis P, Borbe HO, et al. Tolerability and pharmacokinetics of single and multiple doses of azelastine hydrochloride in elderly volunteers. Arzneimittel Forschung 1995; 45 (5): 576-81
87. Kisicki JC, Herman R, Niebch G. Amendment No. 1 to the report: azelastine nasal spray: twenty-nine day tolerability and safety study in healthy subjects. Asta Pharma AG / Carter-Wallace Ltd. CP-90-254; 1993 Apr 23 (Data on file)
88. Wallace Laboratories. Azelastine hydrochloride nasal spray prescribing information. New Jersey, USA, 1997
89. Wober W, Diez Crespo C, Bahre M. Efficacy and tolerability of azelastine nasal spray in the treatment of allergic rhinitis: large scale experience in community practice. Curr Med Res Opin 1997; 13 (10): 617-26
90. MacMahon MT, Newson-Smith G, Granham SP, et al. Intranasal azelastine in seasonal allergic rhinitis [abstract]. Proceedings of the 95th Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics; 1994 Mar 30-Apr 1; New Orleans (LA): 184
91. Boné Calvo J, Botey Sala J, Caballero Goméz L. Long term safety and efficacy of azelastine HCl nasal spray in the treatment of children with perennial allergic rhinitis. Acta Pediatr Esp 1996; 54 (10): 750-64

92. Gastpar H, Dorow P, Aurich R, et al. Investigation of long-term efficacy and tolerability of azelastine nasal spray in the treatment of perennial allergic rhinitis. Arzneimittel Forschung 1993; 43 (7): 771-6

93. Storms WW, Pearlman DS, Chervinsky P, et al. Effectiveness of azelastine nasal solution in seasonal allergic rhinitis. Ear Nose Throat J 1994; 73 (6): 382-6, 390-4

94. Cua-Lim F, Cua PE, Perez A. The efficacy and safety of azelastine nasal spray in perennial allergic rhinitis in Philipinos [abstract]. Allergy 1997; 52 Suppl. 37: 209

95. Weiler JM, Meltzer EO. Azelastine nasal spray as adjunctive therapy to azelastine tablets in the management of seasonal allergic rhinitis. Ann Allergy Asthma Immunol 1997; 79 (4): 327-32

96. Kakiuchi M, Ohashi T, Tanaka K, et al. Central nervous system effects of the novel antiallergic agent HSR-609 and typical antiallergic agents using behavioral and electroencephalographic analyses in dogs. Nihon Shinkei Seishin Yakurigaku Zasshi 1998; 18 (5): 189-99

97. Lassig W, Wober W, Hoflich C, et al. Topical therapy of allergic rhinitis in childhood: allergodil nasal spray-non-sedating in children. Curr Med Res Opin 1996; 13 (7): 391-5

98. Spaeth J, Klimek L, Mosges R. Sedation in allergic rhinitis is caused by the condition and not by antihistamine treatment. Allergy 1996; 51 (12): 893-906

99. Woosley RL, Sale M. QT interval: a measure of drug action. Am J Cardiol 1993; 72 (6): 36B-43B

100. Kanè GC, Lipsky JJ. Drug-grapefruit juice interactions. Mayo Clin Proc 2000; 75 (9): 933-42

101. Bronsky EA, Meltzer EO, Perhach JL, et al. Cardiac safety of azelastine following 8 weeks of intra-nasal administration [abstract]. J Allergy Clin Immunol 1997; 99 (Pt 2): S445

102. DuBuske LM. Second-generation antihistamines: the risk of ventricular arrhythmias. Clin Ther 1999; 21 (2): 281-95

103. Mygind N. Local effect of intranasal beclomethasone dipropionate aerosol in hay fever. BMJ 1973; 4 (5890): 464-6

104. Barnes PJ. Molecular mechanisms of glucocorticoid action in asthma. Pulm Pharmacol Ther 1997; 10 (1): 3-19

105. International Consensus Report on the diagnosis and management of rhinitis: International Rhinitis Management Working Group. Allergy 1994; 49 (19 Suppl): 1-34

106. Dykewicz MS, Fineman S, Nicklas R, et al. Joint task force algorithm and annotations for diagnosis and management of rhinitis. Ann Allergy Asthma Immunol 1998; 81 (5 Pt 2): 469-73

107. van Cauwenberge P, Bachert C, Passalacqua G, et al. Consensus statement on the treatment of allergic rhinitis: European Academy of Allergology and Clinical Immunology. Allergy 2000; 55 (2): 116-34

108. Weiner JM, Abramson MJ, Puy RM. Intranasal corticosteroids versus oral H1 receptor antagonists in allergic rhinitis: systematic review of randomised controlled trials. BMJ 1998; 317 (7173): 1624-9

109. Svensson C, Andersson M, Greiff L, et al. Effects of topical budesonide and levocabastine on nasal symptoms and plasma exudation responses in seasonal allergic rhinitis. Allergy 1998; 53 (4): 367-74

110. Bousquet J, Chanal I, Alquie MC, et al. Prevention of pollen rhinitis symptoms: comparison of fluticasone propionate aqueous nasal spray and disodium cromoglycate aqueous nasal spray: a multicenter, double-blind, double-dummy, parallel-group study. Allergy 1993; 48 (5): 327-33

111. Fisher WG. Comparison of budesonide and disodium cromoglycate for the treatment of seasonal allergic rhinitis in children. Ann Allergy 1994; 73 (6): 515-20

112. Nielsen LP, Mygind N, Dahl R. Intranasal corticosteroids for allergic rhinitis: superior relief? Drugs 2001; 61 (11): 1563-79

113. Aubier M, Levy J, Clerici C, et al. Different effects of nasal and bronchial glucocorticosteroid administration on bronchial hyperresponsiveness in patients with allergic rhinitis. Am Rev Respir Dis 1992; 146 (1): 122-6

114. Corren J, Adinoff AD, Buchmeier AD, et al. Nasal beclomethasone prevents the seasonal increase in bronchial responsiveness in patients with allergic rhinitis and asthma. J Allergy Clin Immunol 1992; 90 (2): 250-6

115. Foresi A, Pelucchi A, Gherson G, et al. Once daily intranasal fluticasone propionate (200 micrograms) reduces nasal symptoms and inflammation but also attenuates the increase in bronchial responsiveness during the pollen season in allergic rhinitis. J Allergy Clin Immunol 1996; 98 (2): 274-82

116. Reed CE, Marcoux JP, Welsh PW. Effects of topical nasal treatment on asthma symptoms. J Allergy Clin Immunol 1988; 81 (5 Pt 2): 1042-7

117. Wood RA, Eggleston PA. The effects of intranasal steroids on nasal and pulmonary responses to cat exposure. Am J Respir Crit Care Med 1995; 151 (2 Pt 1): 315-20

118. Henriksen JM, Wenzel A. Effect of an intranasally administered corticosteroid (budesonide) on nasal obstruction, mouth breathing, and asthma. Am Rev Respir Dis 1984; 130 (6): 1014-8

119. Berkowitz RB, Bernstein DI, LaForce C, et al. Onset of action of mometasone furoate nasal spray (NASONEX) in seasonal allergic rhinitis. Allergy 1999; 54 (1): 64-9

120. Selner JC, Weber RW, Richmond GW, et al. Onset of action of aqueous beclomethasone dipropionate nasal spray in seasonal allergic rhinitis. Clin Ther 1995; 17 (6): 1099-109

121. Holm AF, Fokkens WJ, Godthelp T, et al. A 1-year placebo-controlled study of intranasal fluticasone propionate aqueous nasal spray in patients with perennial allergic rhinitis: a safety and biopsy study. Clin Otolaryngol 1998; 23 (1): 69-73

122. Juniper EF, Guyatt GH, O'Byrne PM, et al. Aqueous beclomethasone diproprionate nasal spray: regular versus "as required" use in the treatment of seasonal allergic rhinitis. J Allergy Clin Immunol 1990; 86 (3 Pt 1): 380-6

123. Banov CH, Woehler TR, LaForce CF, et al. Once daily intranasal fluticasone propionate is effective for perennial allergic rhinitis. Ann Allergy 1994; 73 (3): 240-6

124. Bhatia M, Campbell LM, Ross JR, et al. Intranasal budesonide once daily in seasonal allergic rhinitis. Curr Med Res Opin 1991; 12 (5): 287-95

125. Drouin M, Yang WH, Bertrand B, et al. Once daily mometasone furoate aqueous nasal spray is as effective as twice daily beclomethasone dipropionate for treating perennial allergic rhinitis patients. Ann Allergy Asthma Immunol 1996; 77 (2): 153-60

126. Howarth PH. A comparison of the anti-inflammatory properties of intranasal corticosteroids and antihistamines in allergic rhinitis. Allergy 2000; 55 Suppl. 62: 6-11

127. Esmailpour N, Hogger P, Rohdewald P. Binding of glucocorticoids to human nasal tissue in vitro. Int Arch Allergy Immunol 2000; 122 (2): 151-4

128. Petersen H, Kullberg A, Edsbacker S, et al. Nasal retention of budesonide and fluticasone in man: formation of airway mucosal budesonide-esters in vivo. Br J Clin Pharmacol 2001; 51 (2): 159-63

129. Newman SP, Moren PF, Clarke SW. The nasal distribution of metered dose inhalers. J Laryngol Otol 1987; 101 (2): 127-32
130. Newman SP, Moren F, Clarke SW. Deposition pattern of nasal sprays in man. Rhinology 1988; 26 (2): 111-20
131. Thorsson L, Newman SP, Weisz A, et al. Nasal distribution of budesonide inhaled via a powder inhaler. Rhinology 1993; 31 (1): 7-10
132. Thorsson L, Borga O, Edsbacker S. Systemic availability of budesonide after nasal administration of three different formulations: pressurized aerosol, aqueous pump spray, and powder. Br J Clin Pharmacol 1999; 47 (6): 619-24
133. Daley-Yates PT, Baker RC. Systemic bioavailability of fluticasone propionate administered as nasal drops and aqueous nasal spray formulations. Br J Clin Pharmacol 2001; 51 (1): 103-5
134. Hardy JG, Lee SW, Wilson CG. Intranasal drug delivery by spray and drops. J Pharm Pharmacol 1985; 37 (5): 294-7
135. Bryant ML, Brown P, Gurevich N, et al. Comparison of the clearance of radiolabelled nose drops and nasal spray as mucosally delivered vaccine. Nucl Med Commun 1999; 20 (2): 171-4
136. Argenti D, Colligon I, Heald D, et al. Nasal mucosal inflammation has no effect on the absorption of intranasal triamcinolone acetonide. J Clin Pharmacol 1994; 34 (8): 854-8
137. Greiff L, Andersson M, Svensson J, et al. Absorption across the nasal airway mucosa in house dust mite perennial allergic rhinitis. Clin Physiol Funct Imaging 2002; 22 (1): 55-7
138. Lipworth BJ, Jackson CM. Safety of inhaled and intranasal corticosteroids: lessons for the new millennium. Drug Saf 2000; 23 (1): 11-33
139. Lee DK, Robb FM, Sims EJ, et al. Systemic bioactivity of intranasal triamcinolone and mometasone in perennial allergic rhinitis. Br J Clin Pharmacol 2003; 55 (3): 310-3
140. Wilson AM, Sims EJ, McFarlane LC, et al. Effects of intranasal corticosteroids on adrenal, bone, and blood markers of systemic activity in allergic rhinitis. J Allergy Clin Immunol 1998; 102 (4 Pt 1): 598-604
141. Toft A, Wihl JA, Toxman J, et al. Double-blind comparison between beclomethasone dipropionate as aerosol and as powder in patients with nasal polyposis. Clin Allergy 1982; 12 (4): 391-401
142. LaForce C. Use of nasal steroids in managing allergic rhinitis. J Allergy Clin Immunol 1999; 103 (3 Pt 2): S388-94
143. Graft D, Aaronson D, Chervinsky P, et al. A placebo- and active-controlled randomized trial of prophylactic treatment of seasonal allergic rhinitis with mometasone furoate aqueous nasal spray. J Allergy Clin Immunol 1996; 98 (4): 724-31
144. Andersson M, Berglund R, Greiff L, et al. A comparison of budesonide nasal dry powder with fluticasone propionate aqueous nasal spray in patients with perennial allergic rhinitis. Rhinology 1995; 33 (1): 18-21
145. Soderberg-Warner ML. Nasal septal perforation associated with topical corticosteroid therapy. J Pediatr 1984; 105 (5): 840-1
146. Cervin A, Andersson M. Intranasal steroids and septum perforation – an overlooked complication? A description of the course of events and a discussion of the causes. Rhinology 1998; 36 (3): 128-32
147. Bircher AJ, Pelloni F, Langauer-Messmer S, et al. Delayed hypersensitivity reactions to corticosteroids applied to mucous membranes. Br J Dermatol 1996; 135 (2): 310-3
148. Gonzalo-Garijo MA, Bobadilla-Gonzalez P. Cutaneous-mucosal allergic contact reaction due to topical corticosteroids. Allergy 1995; 50 (10): 833-6
149. Lipworth BJ, Seckl JR. Measures for detecting systemic bioactivity with inhaled and intranasal corticosteroids. Thorax 1997; 52 (5): 476-82
150. Crowley S, Hindmarsh PC, Holownia P, et al. The use of low doses of ACTH in the investigation of adrenal function in man. J Endocrinol 1991; 130 (3): 475-9
151. Homer JJ, Gazis TG. Cushing's syndrome induced by betamethasone nose drops: in rhinological disease betamethasone should be regarded as systemic corticosteroid [letter]. BMJ 1999; 318 (7194): 1355
152. Malozowski S, Purucker M, Worobec A. Cushing's syndrome induced by betamethasone nose drops: children taking intranasal corticosteroids should be monitored for growth retardation [letter]. BMJ 1999; 318 (7194): 1355
153. Findlay CA, Macdonald JF, Wallace AM, et al. Childhood Cushing's syndrome induced by betamethasone nose drops, and repeat prescriptions. BMJ 1998; 317 (7160): 739-40
154. Stevens DJ. Cushing's syndrome due to the abuse of betamethasone nasal drops. J Laryngol Otol 1988; 102 (3): 219-21
155. Nutting CM, Page SR. Iatrogenic Cushing's syndrome due to nasal betamethasone: a problem not to be sniffed at! Postgrad Med J 1995; 71 (834): 231-2
156. Passalacqua G, Albano M, Canonica GW, et al. Inhaled and nasal corticosteroids: safety aspects. Allergy 2000; 55 (1): 16-33
157. Cave A, Arlett P, Lee E. Inhaled and nasal corticosteroids: factors affecting the risks of systemic adverse effects. Pharmacol Ther 1999; 83 (3): 153-79
158. Wilson AM, McFarlane LC, Lipworth BJ. Effects of repeated once daily dosing of three intranasal corticosteroids on basal and dynamic measures of hypothalamic-pituitary-adrenal-axis activity. J Allergy Clin Immunol 1998; 101 (4 Pt 1): 470-4
159. Knutsson U, Stierna P, Marcus C, et al. Effects of intranasal glucocorticoids on endogenous glucocorticoid peripheral and central function. J Endocrinol 1995; 144 (2): 301-10
160. Davies RJ, Nelson HS. Once-daily mometasone furoate nasal spray: efficacy and safety of a new intranasal glucocorticoid for allergic rhinitis. Clin Ther 1997; 19 (1): 27-38
161. Nayak AS, Ellis MH, Gross GN, et al. The effects of triamcinolone acetonide aqueous nasal spray on adrenocortical function in children with allergic rhinitis. J Allergy Clin Immunol 1998; 101 (2 Pt 1): 157-62
162. Howland WC, Dockhorn R, Gillman S, et al. A comparison of effects of triamcinolone acetonide aqueous nasal spray, oral prednisone, and placebo on adrenocortical function in male patients with allergic rhinitis. J Allergy Clin Immunol 1996; 98 (1): 32-8
163. Munk ZM, LaForce C, Furst JA, et al. Efficacy and safety of triamcinolone acetonide aqueous nasal spray in patients with seasonal allergic rhinitis. Ann Allergy Asthma Immunol 1996; 77 (4): 277-81
164. Vargas R, Dockhorn RJ, Findlay SR, et al. Effect of fluticasone propionate aqueous nasal spray versus oral prednisone on the hypothalamic-pituitary-adrenal axis. J Allergy Clin Immunol 1998; 102 (2): 191-7
165. Storms WW. Risk-benefit assessment of fluticasone propionate in the treatment of asthma and allergic rhinitis. J Asthma 1998; 35 (4): 313-36
166. Brannan MD, Herron JM, Reidenberg P, et al. Lack of hypothalamic-pituitary-adrenal axis suppression with once-daily or twice-daily beclomethasone dipropionate aqueous nasal spray

administered to patients with allergic rhinitis. Clin Ther 1995; 17 (4): 637-47

167. Lumry WR. A review of the preclinical and clinical data of newer intranasal steroids used in the treatment of allergic rhinitis. J Allergy Clin Immunol 1999; 104 (4 Pt 1): S150-8
168. Onrust SV, Lamb HM. Mometasone furoate: a review of its intranasal use in allergic rhinitis. Drugs 1998; 56 (4): 725-45
169. Grossman J, Banov C, Bronsky EA, et al. Fluticasone propionate aqueous nasal spray is safe and effective for children with seasonal allergic rhinitis. Pediatrics 1993; 92 (4): 594-9
170. Lipworth BJ. Systemic adverse effects of inhaled corticosteroid therapy: a systematic review and meta-analysis. Arch Intern Med 1999; 159 (9): 941-55
171. Fokkens WJ, van de Merwe JP, Braat JP, et al. The effect of intranasal and inhaled corticosteroids in healthy volunteers on the number of circulating lymphocytes and lymphocyte subsets. Allergy 1999; 54 (2): 158-64
172. Wilson AM, Lipworth BJ. 24-Hour and fractionated profiles of adrenocortical activity in asthmatic patients receiving inhaled and intranasal corticosteroids. Thorax 1999; 54 (1): 20-6
173. Daley-Yates PT. Pharmacokinetic (PK) and pharmacodynamic (PD) data for inhaled and intranasal corticosteroids (CS) reassessed using a physiological PK/PD model [abstract]. Eur Respir J 2001; 18 Suppl. 33: 147S
174. Skoner DP, Rachelefsky GS, Meltzer EO, et al. Detection of growth suppression in children during treatment with intranasal beclomethasone dipropionate [abstract]. Pediatrics 2000; 105 (2): E23
175. Wolthers OD, Pedersen S. Knemometric assessment of systemic activity of once daily intranasal dry-powder budesonide in children. Allergy 1994; 49 (2): 96-9
176. Richards DH, Daley-Yates PT. Choice of inhaled and intranasal steroids when used in combination for asthma and rhinitis in children [abstract]. Allergy 2000; 55 Suppl. 63: A185
177. Agertoft L, Pedersen S. Short-term lower leg growth rate in children with rhinitis treated with intranasal mometasone furoate and budesonide. J Allergy Clin Immunol 1999; 104 (5): 948-52
178. Schenkel EJ, Skoner DP, Bronsky EA, et al. Absence of growth retardation in children with perennial allergic rhinitis after one year of treatment with mometasone furoate aqueous nasal spray [abstract]. Pediatrics 2000; 105 (2): E22
179. Scadding GK, Richards DH. Steroid selection can reduce potential for steroid load [electronic letter]. British Medical Journal [online]. Available from URL: http//bmj.com/cgi/eletters/324/7350/1374 [Accessed 2002 Jul 27]
180. Kallen B, Rydhstroem H, Aberg A. Congenital malformations after the use of inhaled budesonide in early pregnancy. Obstet Gynecol 1999; 93 (3): 392-5
181. Edelman DA, van Os WAA. Safety of intranasal beclomethasone dipropionate: a review. Respir Care 1996, 30
182. Edwards TB. Effectiveness and safety of beclomethasone dipropionate, an intranasal corticosteroid, in the treatment of patients with allergic rhinitis. Clin Ther 1995; 17 (6): 1032-41
183. Daley-Yates PT, Price AC, Sisson JR, et al. Beclomethasone dipropionate: absolute bioavailability, pharmacokinetics and metabolism following intravenous, oral, intranasal and inhaled administration in man. Br J Clin Pharmacol 2001; 51 (5): 400-9
184. Wihl JA, Andersson KE, Johansson SA. Systemic effects of two nasally administered glucocorticosteroids. Allergy 1997; 52 (6): 620-6
185. Rachelefsky GS, Chervinsky P, Meltzer EO, et al. An evaluation of the effects of beclomethasone dipropionate aqueous nasal spray [Vancenase AQ (VNS)] on long-term growth in children [abstract]. J Allergy Clin Immunol 1998; 101: 978A
186. Fraunfelder FT, Meyer SM. Posterior subcapsular cataracts associated with nasal or inhalation corticosteroids. Am J Ophthalmol 1990; 109 (4): 489-90
187. Derby L, Maier WC. Risk of cataract among users of intranasal corticosteroids. J Allergy Clin Immunol 2000; 105 (5): 912-6
188. Garbe E, LeLorier J, Boivin JF, et al. Inhaled and nasal glucocorticoids and the risks of ocular hypertension or open-angle glaucoma. JAMA 1997; 277 (9): 722-7
189. GDS/96/044, GlaxoSmithKline, 1996 (Data on file)
190. Mygind N. Effects of beclomethasone dipropionate aerosol on nasal mucosa. Br J Clin Pharmacol 1977; 4 Suppl. 3: 287S-91S
191. Mygind N, Sorensen H, Pedersen CB. The nasal mucosa during long-term treatment with beclomethasone dipropionate aerosol: a light-and scanning electron microscopic study of nasal polyps. Acta Otolaryngol 1978; 85 (5-6): 437-43
192. WPSP/01/032, GlaxoSmithKline, 2001 (Data on file)
193. Beconase Patient Information Leaflet, GlaxoSmithKline
194. GSK Key Opinion Leader Development Programme, GlaxoSmithKline, 2002 (Data on file)
195. Synnerstad B, Lindqvist N. A clinical comparison of intranasal budesonide with beclomethasone dipropionate for perennial non-allergic rhinitis: a 12 month study. Br J Clin Pract 1996; 50 (7): 363-6
196. Lindqvist N, Balle VH, Karma P, et al. Long-term safety and efficacy of budesonide nasal aerosol in perennial rhinitis: a 12-month multicentre study. Allergy 1986; 41 (3): 179-86
197. Pipkorn U, Pukander J, Suonpaa J, et al. Long-term safety of budesonide nasal aerosol: a 5.5-year follow-up study. Clin Allergy 1988; 18 (3): 253-9
198. Wolthers OD, Pedersen S. Short-term growth in children with allergic rhinitis treated with oral antihistamine, depot and intranasal glucocorticosteroids. Acta Paediatr 1993; 82 (8): 635-40
199. Dent G. Ciclesonide (Byk Gulden). Curr Opin Investig Drugs 2002; 3 (1): 78-83
200. Schmidt BM, Timmer W, Georgens AC, et al. The new topical steroid ciclesonide is effective in the treatment of allergic rhinitis. J Clin Pharmacol 1999; 39 (10): 1062-9
201. Weinbrenner A, Huneke D, Zschiesche M, et al. Circadian rhythm of serum cortisol after repeated inhalation of the new topical steroid ciclesonide. J Clin Endocrinol Metab 2002; 87 (5): 2160-3
202. Physicians Desk Reference. 52nd ed. Medical Economics Company; 1998. Nasarel (flunisolide) Nasal Solution, 0.025%. Montvale (NJ). 889-91
203. Gillman SA, Anolik R, Schenkel E, et al. One-year trial on safety and normal linear growth with flunisolide HFA in children with asthma. Clin Pediatr (Phila) 2002; 41 (5): 333-40
204. Harding SM. The human pharmacology of fluticasone propionate. Respir Med 1990; 84 Suppl. A: 25-9
205. van As A, Bronsky E, Grossman J, et al. Dose tolerance study of fluticasone propionate aqueous nasal spray in patients with seasonal allergic rhinitis. Ann Allergy 1991; 67 (2 Pt 1): 156-62
206. Bronsky EA, Dockhorn RJ, Meltzer EO, et al. Fluticasone propionate aqueous nasal spray compared with terfenadine tablets in the treatment of seasonal allergic rhinitis. J Allergy Clin Immunol 1996; 97 (4): 915-21

207. Gulant SP, Ahrens RC, Dockhorn RJ, et al. Treatment of seasonal allergic rhinitis with once-daily intranasal fluticasone propionate therapy in children: Fluticasone Propionate Collaborative Pediatric Working Group. J Pediatr 1994; 125 (4): 628-34
208. ~~Howland WC. Fluticasone propionate: topical or systemic effects?~~ Clin Exp Allergy 1996; 26 Suppl. 3: 18-22
209. BL2001/00003/00, GlaxoSmithKline, 2001 (Data on file)
210. Konig P, Ford L, Galant S, et al. A 1-year comparison of the effects of inhaled fluticasone propionate (FP) and placebo on growth in prepubescent children with asthma [abstract]. Eur Respir J 1996; 9 (294s): 1860
211. Bond DW, Charlton CP, Gregson RM. Drug points: benign intracranial hypertension secondary to nasal fluticasone propionate. BMJ 2001; 322 (7291): 897
212. Chen CC, Baroody FM, Reed KD, et al. Effects of one year treatment with fluticasone propionate aqueous nasal spray (FPANS) and terfenadine (TER) on the nasal mucosa: a safety study using electron and light microscopy [abstract no. S497]. J Allergy Clin Immunol 1997; 99 (1 Pt 2): 2013
213. ~~Braat JP, Ainge G, Bowles JA, et al. The lack of effect of~~ benzalkonium chloride on the cilia of the nasal mucosa in patients with perennial allergic rhinitis: a combined functional, light, scanning and transmission electron microscopy study. Clin Exp Allergy 1995; 25 (10): 957-65
214. Scadding GK, Lund VJ, Holmstrom M, et al. Clinical and physiological effects of fluticasone propionate aqueous nasal spray in the treatment of perennial rhinitis. Rhinol Suppl 1991; 11: 37-43
215. BL2001/00003/00, GlaxoSmithKline, 2001 (Data on file)
216. Flixonase Summary of Product Characteristics, GlaxoSmithKline
217. Flixonase Medical Workshop Proceedings, London: Synergy Medical Education, 2002 Dec
218. GlaxoSmithKline Clinical Expert Report for Flixonase, GlaxoSmithKline, 2001
219. GlaxoSmithKline Safety Reports WSP/99/010 and WPSP/99/037, GlaxoSmithKline, 1999
220. Brannan MD, Seiberling M, Cutler DL, et al. Lack of systemic activity with intranasal mometasone furoate. J Allergy Clin Immunol 1996; 97 (1 Pt 3): 198
221. Brannan MD, Herron JM, Affrime MB. Safety and tolerability of once-daily mometasone furoate aqueous nasal spray in children [abstract]. Clin Ther 1997; 19 (6): 1330-9
222. Meltzer EO, Berger WE, Berkowitz RB, et al. A dose-ranging study of mometasone furoate aqueous nasal spray in children with seasonal allergic rhinitis. J Allergy Clin Immunol 1999; 104 (1): 107-14
223. Dibildox J. Safety and efficacy of mometasone furoate aqueous nasal spray in children with allergic rhinitis: results of recent clinical trials. J Allergy Clin Immunol 2001; 108 (1 Suppl.): S54-8
224. Minshall E, Ghaffar O, Cameron L, et al. Assessment by nasal biopsy of long-term use of mometasone furoate aqueous nasal spray (Nasonex) in the treatment of perennial rhinitis. Otolaryngol Head Neck Surg 1998; 118 (5): 648-54
225. Meltzer EO, Jalowayski AA, Orgel HA, et al. Subjective and objective assessments in patients with seasonal allergic rhinitis: effects of therapy with mometasone furoate nasal spray. J Allergy Clin Immunol 1998; 102 (1): 39-49
226. Welch MJ, Bronsky E, Findlay S, et al. Long-term safety of triamcinolone acetonide nasal aerosol for the treatment of perennial allergic rhinitis. Clin Ther 1994; 16 (2): 253-62
227. Koepke JW, Beaucher WN, Kobayashi RH, et al. Long-term safety and efficacy of triamcinolone acetonide aqueous nasal spray for the treatment of perennial allergic rhinitis. Allergy Asthma Proc 1997; 18 (1): 33-7
228. Feiss G, Morris R, Rom D, et al. A comparative study of the ~~effects of intranasal triamcinolone acetonide aerosol (ITAA)~~ and prednisone on adrenocortical function. J Allergy Clin Immunol 1992; 89 (6): 1151-6
229. Tinkelman D, Falliers C, Gross G, et al. Multicenter evaluation of triamcinolone acetonide nasal aerosol in the treatment of adult patients with seasonal allergic rhinitis. Ann Allergy 1990; 64 (2 Pt 2): 234-40
230. Spector S, Bronsky E, Chervinsky P, et al. Multicenter, double-blind, placebo-controlled trial of triamcinolone acetonide nasal aerosol in the treatment of perennial allergic rhinitis. Ann Allergy 1990; 64 (3): 300-5
231. Settipane G, Korenblat PE, Winder J, et al. Triamcinolone acetonide aqueous nasal spray in patients with seasonal ragweed allergic rhinitis: a placebo-controlled, double-blind study. Clin Ther 1995; 17 (2): 252-63
232. ~~Storms W, Bronsky E, Findlay S, et al. Once daily triamci-~~ nolone acetonide nasal spray is effective for the treatment of perennial allergic rhinitis. Ann Allergy 1991; 66 (4): 329-34
233. Laliberte F, Laliberte MF, Lecart S, et al. Clinical and pathologic methods to assess the long-term safety of nasal corticosteroids: French Triamcinolone Acetonide Study Group. Allergy 2000; 55 (8): 718-22
234. Klossek JM, Laliberte F, Laliberte MF, et al. Local safety of intranasal triamcinolone acetonide: clinical and histological aspects of nasal mucosa in the long-term treatment of perennial allergic rhinitis. Rhinology 2001; 39 (1): 17-22
235. Passali D, Mosges R, Hassan H, et al. International Conference on Allergic Rhinitis in Childhood. Allergy 1999; 54 Suppl. 55: 4-34
236. Warner JO. Early treatment of the atopic child. Pediatr Allergy Immunol 1997; 8 (10 Suppl.): 46-8
237. Iikura Y, Naspitz CK, Mikawa H, et al. Prevention of asthma by ketotifen in infants with atopic dermatitis. Ann Allergy 1992; 68 (3): 233-6
238. Vuurman EF, van Veggel LM, Uiterwijk MM, et al. Seasonal allergic rhinitis and antihistamine effects on children's learning. Ann Allergy 1993; 71 (2): 121-6
239. Ellegard E, Karlsson G. Nasal congestion during the menstrual cycle. Clin Otolaryngol 1994; 19 (5): 400-3
240. Ellegard E, Karlsson G. Nasal congestion during pregnancy. Clin Otolaryngol 1999; 24 (4): 307-11
241. Ellegard E, Karlsson G. IgE-mediated reactions and hyperreactivity in pregnancy rhinitis. Arch Otolaryngol Head Neck Surg 1999; 125 (10): 1121-5
242. Greenberger PA, Patterson R. Beclomethasone diproprionate for severe asthma during pregnancy. Ann Intern Med 1983; 98 (4): 478-80
243. Saxen I. Cleft palate and maternal diphenhydramine intake [letter]. Lancet 1974; I (7854): 407-8
244. Saxen I. Associations between oral clefts and drugs taken during pregnancy. Int J Epidemiol 1975; 4 (1): 37-44
245. Einarson A, Bailey B, Jung G, et al. Prospective controlled study of hydroxyzine and cetirizine in pregnancy. Ann Allergy Asthma Immunol 1997; 78 (2): 183-6
246. Yanez A, Rodrigo GJ. Intranasal corticosteroids versus topical H1 receptor antagonists for the treatment of allergic rhinitis: a systematic review with meta-analysis. Ann Allergy Asthma Immunol 2002; 89 (5): 479-84

247. Foresi A. A comparison of the clinical efficacy and safety of intranasal fluticasone propionate and antihistamines in the treatment of rhinitis. Allergy 2000; 55 Suppl. 62: 12-4
248. Allen DB. Do intranasal corticosteroids affect childhood growth? Allergy 2000; 55 Suppl. 62: 15-8
249. van Bavel J, Findlay SR, Hampel FC, et al. Intranasal fluticasone propionate is more effective than terfenadine tablets for seasonal allergic rhinitis. Arch Intern Med 1994; 154 (23): 2699-704
250. Trangsrud AJ, Whitaker AL, Small RE. Intranasal corticosteroids for allergic rhinitis. Pharmacotherapy 2002; 22 (11): 1458-67
251. Kaszuba SM, Baroody FM, deTineo M, et al. Superiority of an intranasal corticosteroid compared with an oral antihistamine in the as-needed treatment of seasonal allergic rhinitis. Arch Intern Med 2001; 161 (21): 2581-7

Correspondence and offprints: Dr *Rami Jean Salib*, Respiratory Cell and Molecular Biology Sub-Division, Infection, Inflammation and Repair, Centre Block (MP 810), Southampton General Hospital, Tremona Road, Southampton, SO16 6YD, UK.
E-mail: rjs4@soton.ac.uk

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]

EXHIBIT 1005(K)

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 vascomotor 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 v1/4137.04700

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.

EXHIBIT 1005(L)

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. ________________

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/518,016	07/06/2005	Amar Lulla	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. 10/518,016	Applicant(s) LULLA ET AL.	
	Examiner THOR NIELSEN	Art Unit 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.** 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 *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

EXHIBIT 1005(M)

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. ________________

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/518,016	07/06/2005	Amar Lulla	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