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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

ASTRAZENECA LP and ASTRAZENECA AB, Plaintiffs, v. APOTEX, INC. and APOTEX CORP., Defendants.	Civil Action No. 1:09-cv-1518 (RMD)(AMD)

AMENDED COMPLAINT FOR DECLARATORY JUDGMENT

Plaintiffs AstraZeneca LP and AstraZeneca AB (collectively "AstraZeneca") for their Amended Complaint for a declaratory judgment of patent infringement against Apotex, Inc. and Apotex Corp. (collectively, "Apotex" or "Defendants"), aver as follows:

THE PARTIES

1. AstraZeneca LP is a limited partnership organized and existing under the laws of the State of Delaware, having its principal place of business at 1800 Concord Pike, Wilmington, Delaware.

2. AstraZeneca AB is a company organized and existing under the laws of Sweden, having its principal place of business at S 151 85 Södertälje, Sweden.

3. AstraZeneca LP is the holder of an approved New Drug Application ("NDA"), No. 20-929, for the manufacture and sale of budesonide inhalation suspension for the maintenance treatment of asthma and as a prophylactic therapy in children 12 months to 8 years of age. AstraZeneca markets and sells this composition in the United States under the trade name PULMICORT RESPULES® (budesonide inhalation suspension).

4. Upon information and belief, defendant Apotex, Inc. is a corporation organized and existing under the laws of Canada, having a place of business at 150 Signet Drive, Toronto, Ontario, Canada M9L 1T9.

5. Upon information and belief, defendant Apotex Corp. is a corporation organized and existing under the laws of the State of Delaware, having a place of business at 2400 N. Commerce Parkway, Suite 400, Weston, Florida.

JURISDICTION AND VENUE

6. This is an action seeking a declaration of patent infringement arising under the Declaratory Judgment Act, Title 28, United States Code, §§ 2201, 2202 and the patent laws of the United States, Title 35, United States Code.

7. This Court has original jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a), and under the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202, because this action involves an actual controversy concerning the infringement of the patents-in-suit.

8. This Court has personal jurisdiction over Defendants. Upon information and belief, Defendants have maintained continuous and systematic contacts with the State of New Jersey, including by shipping, distributing, offering for sale and selling their products, directly or through intermediaries (including distributors, retailers, pharmacists, doctors, and others), in the State of New Jersey. Upon information and belief, Defendants have previously consented to personal jurisdiction of this Court on multiple occasions and have previously availed themselves of this Court by filing suit and asserting counterclaims in other civil actions initiated in this jurisdiction. Upon information and belief, Apotex Corp. has registered under Reg. #5003192 with the New Jersey Department of Health and Senior Services as a "Drug or Medical Device Manufacturing or Wholesale Drug or Medical Device Business" pursuant to N.J. Stat. Ann. 24:6B.

9. Venue is proper in this District under 28 U.S.C. §§ 1391(b), (c) and (d), and 1400(b).

THE PATENTS IN SUIT

10. AstraZeneca AB is the lawful owner of all right, title, and interest in and to the following United States patents, including all right to sue and to recover for past infringement thereof, which patents contain one or more claims covering the method of use and packaging of PULMICORT RESPULES®.

A. United States Patent No. 6,598,603, entitled "METHOD FOR TREATING RESPIRATORY DISEASES" ("the '603 patent"), a copy of which is attached hereto as Exhibit A, which was duly and legally issued July 29, 2003, naming Bertil Andersson, Thor-Björn Conradsson, and Göran Eriksson as the inventors.

B. United States Patent No. 6,899,099, entitled "METHOD FOR TREATING A RESPIRATORY DISEASE" ("the '099 patent"), a copy of which is attached hereto as Exhibit B, which was duly and legally issued May 31, 2005, naming Bertil Andersson, Thor-Björn Conradsson, and Göran Eriksson as the inventors.

C. United States Patent No. 7,524,834, entitled "STERILE POWDERS, FORMULATIONS, AND METHODS FOR PRODUCING THE SAME" ("the '834 patent"), a copy of which is attached hereto as Exhibit C, which was duly and legally issued April 28, 2009, naming Ann-Kristin Karlsson, Cheryl Larrivee-Elkins, and Ove Molin as the inventors.

APOTEX'S ANDA FOR BUDESONIDE INHALATION SUSPENSION

11. Upon information and belief, subject to Fed. R. Civ. P. 11(b)(3), Apotex has submitted an Abbreviated New Drug Application ("ANDA") to the U.S. Food and Drug Administration ("FDA"), under Title 21, United States Code, § 355(j) (§ 505(j) of the Federal Food, Drug and Cosmetic Act), in order to obtain approval to engage in the commercial

manufacture, use, sale and/or importation of a generic version of PULMICORT RESPULES® budesonide inhalation suspension.

12. Upon information and belief, subject to Fed. R. Civ. P. 11(b)(3), Apotex's ANDA contains information to show that its budesonide inhalation suspension (a) is bioequivalent to PULMICORT RESPULES®, (b) has the same active ingredient as PULMICORT RESPULES®, (c) has the same route of administration, dosage form, and strength as PULMICORT RESPULES®, and (d) has the same, or substantially the same, proposed labeling as PULMICORT RESPULES®.

13. Upon information and belief, subject to Fed. R. Civ. P. 11(b)(3), Apotex's budesonide inhalation suspension, its package insert, and/or its use are the subject of one or more claims of the '603, '099, and '834 patents.

14. On or about March 18, 2009, representatives from Apotex informed AstraZeneca that FDA approval of Apotex's ANDA for a generic version of PULMICORT RESPULES® was expected within two weeks. These same representatives from Apotex further informed AstraZeneca that Apotex intended to launch its generic version of PULMICORT RESPULES® in the United States immediately upon receipt of FDA approval.

15. Upon information and belief, subject to Fed. R. Civ. P. 11(b)(3), Apotex has now received FDA approval for its generic version of PULMICORT RESPULES® and communicated same to AstraZeneca via email on or about March 30, 2009. Apotex further communicated on or about March 30, 2009 that its generic product is an equivalent to AstraZeneca's PULMICORT RESPULES® and that Apotex is ready and able to commence sale in the United States immediately. Upon such sale of Apotex's generic product, Apotex will be infringing the '603, '099, and '834 patents.

JUSTICIABLE CONTROVERSY

16. By virtue of, *inter alia*, the facts alleged in paragraphs 11-15, there exists an actual and justiciable case or controversy between the parties as to whether Apotex will infringe the '603, '099, and '834 patents. AstraZeneca accordingly is entitled by law to bring and maintain this action for declaratory judgment under, *inter alia*, the Declaratory Judgment Act.

COUNT I
(Declaratory Judgment of Infringement of the '603, '099, and '834 Patents)

17. AstraZeneca refers to and incorporates herein the allegations of Paragraphs 1-15 above.

18. There is an actual and justiciable case or controversy between AstraZeneca and Apotex regarding the infringement of the '603, '099, and '834 patents.

19. Upon information and belief, subject to Fed. R. Civ. P. 11(b)(3), Apotex's manufacture, use, sale, offer for sale, and/or importation of its generic budesonide inhalation suspension will infringe, contribute to the infringement of, and/or induce the infringement of one or more claims of the '603, '099, and '834 patents.

20. AstraZeneca is entitled to a declaration that Apotex's manufacture, use, sale, offer for sale, and/or importation of its generic budesonide inhalation suspension will infringe, contribute to the infringement of, and/or induce the infringement of one or more claims of the '603, '099, and '834 patents.

21. Upon information and belief, Apotex has been aware of the existence of the '603, '099, and '834 patents, and has no reasonable basis for believing that Apotex's generic budesonide inhalation suspension will not infringe one or more claims of the '603, '099, and '834 patents. This infringement by the defendant will be willful and deliberate and in disregard

of AstraZeneca's lawful rights under the '603, '099, and '834 patents, thus rendering this case "exceptional", as that term is set forth in 35 U.S.C. § 285.

22. The acts of infringement by Defendants set forth above will cause AstraZeneca irreparable harm for which it has no adequate remedy at law, including irreparable harm within the State of New Jersey and this Judicial District, and will continue unless preliminarily and permanently enjoined by this Court.

RELIEF

WHEREFORE, AstraZeneca requests entry of judgment in its favor and against Apotex as follows:

A. Declaring that the '603, '099, and '834 patents are valid and enforceable;

B. Declaring that Apotex's budesonide inhalation suspension and its use will infringe the '603, '099, and '834 patents;

C. Preliminarily and permanently enjoining, pursuant to 35 U.S.C. § 283 and Fed. R. Civ. P. 65, the defendants, their officers, agents, servants, employees, parents, subsidiaries, affiliate corporations, other related business entities and all other persons acting in concert, participation, or in privity with them, and their successors or assigns, from any commercial manufacture, use, offer to sell or sale within the United States, or importation into the United States, of any drug product that infringes the '603, '099, and '834 patents;

D. Declaring this an exceptional case and awarding AstraZeneca its attorney fees, as provided by 35 U.S.C. §§ 271(e)(4) and 285; and

E. Such other and further relief as the Court may deem just and proper.

Respectfully submitted,

Dated: May 8, 2009

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that true copies of Plaintiffs' Amended Complaint with supporting papers were caused to be served via ECF and e-mail upon the following:

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EXHIBIT A

US006598603B1

(12) **United States Patent**
Andersson et al.

(10) **Patent No.: US 6,598,603 B1**
(45) **Date of Patent: Jul. 29, 2003**

(54) **METHOD FOR TREATING RESPIRATORY DISEASES**

(75) Inventors: **Bertil Andersson**, Bjärred (SE); **Thor-Björn Conradsson**, Södra Sandby (SE); **Göran Eriksson**, Dalby (SE)

(73) Assignee: **Astra Aktiebolag** (SE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/220,137**

(22) Filed: **Dec. 23, 1998**

Related U.S. Application Data

(60) Provisional application No. 60/070,291, filed on Dec. 31, 1997.

(51) **Int. Cl.**[7] **A61M 15/00**

(52) **U.S. Cl.** **128/200.24**; 128/200.14; 128/203.12

(58) **Field of Search** 128/200.14, 200.23, 128/203.12, 203.15

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(List continued on next page.)

Primary Examiner—Aaron J. Lewis
(74) *Attorney, Agent, or Firm*—Fish & Richardson P.C.

(57) **ABSTRACT**

The invention provides a novel method of treating respiratory diseases, e.g., pediatric asthma, in a continuing regimen with not more than one daily dose of the drug budesonide using a nebulizer.

30 Claims, No Drawings

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METHOD FOR TREATING RESPIRATORY DISEASES

This application claims benefit of provisional application Ser. No. 60/070,291 filed Dec. 31, 1997.

BACKGROUND OF THE INVENTION

The invention relates to the treatment of respiratory diseases.

There is significant difficulty in the treatment of young children, including infants, who suffer from respiratory diseases, e.g., asthma. In light of the requirement for frequent and repeated administration of appropriate drugs, issues of compliance and convenience are major aspects of this problem. Furthermore, current methods of intrapulmonary delivery of drugs, e.g., glucocorticosteroids (GCS), are not optimal for use in infants and young children.

SUMMARY OF THE INVENTION

The invention provides a new method of treating respiratory diseases such as asthma that involves administering a budesonide composition with a nebulizer not more than once per day. This administration regimen improves compliance and convenience, both significant factors in treating these diseases, particularly in infants and young children. Moreover, the nebulizer is readily and effectively used with infants as well as young children.

Specifically, the invention features a method of treating a patient suffering from a respiratory disease in which a composition, e.g., a suspension, of budesonide is administered by nebulization at a frequency of between once per day and once per month in a continuing regimen. For example, the frequency of administration can be once and only once per day, or once and only once every two days. The doses can be, e.g., 0.05 mg to 15 mg, 0.1 mg to 2.0 mg, or 0.25 mg to 1.0 mg budesonide. The drug can be provided as an aqueous suspension in which the budesonide is suspended in a solvent containing about 0.05 mg to 0.15 mg sodium edetate, about 8.0 mg to 9.0 mg sodium chloride, about 0.15 mg to 0.25 mg polysorbate, about 0.25 mg to 0.30 mg anhydrous citric acid, and about 0.45 mg to 0.55 mg sodium citrate per 1 ml of water.

This new method of treatment can be used in patients suffering from respiratory diseases that include, for example, inflammatory airway diseases, croup, and bronchopulmonary dysplasia. Inflammatory airway diseases include asthma, chronic obstructive pulmonary disease (COPD), and bronchiolitis. Patients can be any age from birth, e.g., newborn, one day to fifteen years old, one month to eight years old, or six months to five years old. The method is also effective in older patients.

A "continuing regimen," is a treatment regimen of a series of two or more administrations that occur over days, weeks, months, or years. The dosage of each administration can be the same or varied throughout the continuing regimen.

The doses of budesonide specified for administration by nebulization are those added to the nebulizing device. In a typical situation, approximately 40% to 60% of the drug actually leaves the nebulizer, and of this only approximately 25% (i.e., 10% to 15% of the nominal dose) is delivered to the patient. This is because the drug is delivered constantly, and when the patient is exhaling, the drug leaving the nebulizer will not be delivered to the patient; it will instead be lost to the environment. Of the amount delivered to the patient, approximately 6% to 9% of the nominal dose is delivered to the lungs.

The invention also features a kit for treating respiratory diseases, the kit including a budesonide composition in a sealed container, the composition including 0.05 mg to 15 mg budesonide and a solvent, and a label indicating administration by nebulization in a continuing regimen at a frequency of not more than once per day.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. All publications, patent applications, patents and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

Other features and advantages of the invention, e.g., treatment of childhood asthma, will be apparent from the following description and from the claims.

DETAILED DESCRIPTION

The invention is a convenient yet highly effective method of treating asthma involving not more than one administration per day in a continuing dosage regimen. This new method represents a significant advantage, particularly in infants and young children in which it is frequently difficult to achieve compliance with treatments involving more frequent administrations. Such treatments can involve the use of portable propellant-based inhalers which a young child can either use improperly, lose, or be embarrassed to use in front of his or her peers. Once a day or less frequent treatments are cost effective and result in an improved quality of life. In general, a patient (or a patient's family) can choose a time of administration that is convenient for them.

In infants, standard inhalation devices are technically difficult to use. The fact that in the new method the drug can be delivered by a mask applied over the infant's nose and mouth obviates this problem. In addition, in using the nebulizer for administration, the drug is constantly pumped into the face mask. Thus, effective drug delivery does not require constant and deep inhalation. This aspect of the treatment is also advantageous in, for example, incapacitated or neurologically impaired patients.

Two randomized, double-blind, placebo-controlled, twelve-week studies assessed the efficacy and safety of budesonide in children six months to eight years of age who had persistent asthma that was not effectively controlled by non-GCS therapies. The budesonide suspended in a solvent (or a placebo) was administered once per day by a nebulizer connected to a compressor. This treatment resulted in statistically significant improvements in asthma symptoms and a decrease in the number of days in which auxiliary bronchodilator medication was used. Furthermore, there were no significant differences between treatment groups in the type, incidence, or severity of adverse events. There were also no apparent differences between the groups in changes observed in physical examinations, clinical laboratory tests, or oropharyngeal or nasal fungal cultures. Measurement of adrenocorticotropic hormone (ACTH)-induced plasma cortisol levels showed no evidence of hypothalamus-pituitary-adrenal (HPA)-axis suppression by budesonide after twelve weeks of treatment. In summary, these results demonstrated both the efficacy and safety of budesonide when administered to children once per day.

After it has been taken up by airway cells, budesonide forms conjugates (esters) with long-chain fatty acids such as oleic acid. Unlike free budesonide, the budesonide conjugates are inactive as they do not bind to the GCS receptor. However, the conjugation of budesonide is a reversible process. As the concentration of free budesonide in the airway cells falls, the conjugates undergo lipolysis, and further free budesonide is produced, thus maintaining the level available for receptor binding. Intracellular conjugated budesonide thus acts as a "depot" of free budesonide in the airway cells, prolonging the local effect of the compound. This proposed mechanism of action is exemplary; the invention is not limited by any particular mechanism of action.

Methods of Treating Respiratory Diseases

The invention features a new method for treating a patient suffering from a respiratory disease using the drug budesonide which is administered to the patient not more frequently than once per day. It can be delivered, for example, once a day, once every 1.5 days, once every 2 days, once every 3 days, once a week, once every two weeks, or once a month. Treatment is in a continuing regimen for as long as required.

The drug can be delivered dispersed in a solvent, e.g., in the form of a solution or a suspension. It can be suspended in an appropriate physiological solution, e.g., physiological saline or a buffered solution containing 0.05 mg to 0.15 mg disodium edetate, 8.0 mg to 9.0 mg NaCl, 0.15 mg to 0.25 mg polysorbate, 0.25 mg to 0.30 mg anhydrous citric acid, and 0.45 mg to 0.55 mg sodium citrate per 1 ml of water so as to achieve a pH of about 4.0 to 5.0. The budesonide suspension can made, for example, from micronized budesonide.

The therapeutic suspensions can also contain one or more excipients. Excipients are well known in the art and include buffers (e.g., citrate buffer, phosphate buffer, acetate buffer and bicarbonate buffer), amino acids, urea, alcohols, ascorbic acid, phospholipids, proteins (e.g., serum albumin), EDTA, sodium chloride, liposomes, mannitol, sorbitol, and glycerol. Solutions or suspensions can be encapsulated in liposomes or biodegradable microspheres.

The budesonide suspension is provided in a substantially sterile form by, for example, dry-heating the budesonide powder for 2 to 6 hours at 90° C. to 150° C. and employing sterile manufacture for the rest of the process. This involves production and sterilization by filtration of the buffered solvent solution used for the suspension, aseptic suspension of the budesonide in the sterile buffered solvent solution, and dispensing of the suspension into sterile receptacles by methods familiar to those of ordinary skill in the art. This process results in a sterility assurance of 6 as required by the Food and Drug Administration of the U.S. government.

The route of administration is intrapulmonary and the drug is delivered in a nebulized composition by, for example, a nebulizer connected to a compressor (e.g., the Pari LC-Jet Plus® nebulizer connected to a Pari Master® compressor manufactured by Pari Respiratory Equipment, Inc., Richmond, Va.).

Patients are those suffering form a respiratory disease. Relevant respiratory diseases include inflammatory airway diseases, croup, and bronchopulmonary dysplasia. Examples of inflammatory airway diseases include asthma, COPD and bronchiolitis.

Patients can be of either sex. They can be treated by the new method at any age from birth. They can, for example be treated as early as thirty minutes after birth. The patients can also much older, e.g., twelve months, two years, four years, then years, forty years, or even seventy years of age, or older. Patients can be six months to five or eight years old.

Doses of budesonide can be the same, or can be varied, for patients of all age groups and all sizes and weights. When administered as a nebulized suspension, the dose can be, e.g., 0.05 mg to 15 mg, 0.1 mg to 2.0 mg, or 0.25 mg to 1.0 mg by budesonide per administration. Evening administration can result in better control of nocturnal and early morning symptoms which are frequent problems in asthma. If excess budesonide is used in a single administration, it is unlikely that harmful effects will occur.

Nebulizable budesonide is provided, for example, as single dose units (e.g., sealed plastic containers or vials) packed in foil envelopes. Each vial contains a unit dose (e.g., 0.25 mg, 0.5 mg, or 1.0 mg) of micronized budesonide suspended in a volume, e.g., 2 ml, of solvent. The unit dose or, if desired and directed by a physician, a fraction of the unit dose is added to the nebulizer. Patients should rinse out their mouths with water after administration of each dose.

Where diseases other than asthma are to be treated with solvent dispersed budesonide, optimal doses can be established by methods familiar to those in the art, e.g., methods analogous to those described in Examples 1 and 2. Doses, for example, for COPD, bronchiolitis, croup, and bronchopulmonary dysplasia, as in asthma, can generally be 0.05 to 15 mg, 0.1 mg to 2.0 mg, or 0.25 mg to 1.0 mg budesonide per administration.

The following examples are meant to illustrate, not limit, the invention.

EXAMPLES

Example 1

A Phase III Study of Three Dose Levels of Once-A-Day Budesonide Nebulizing Suspension and Placebo in Asthmatic Children

Objectives

The objectives of the study were to compare the relative efficacy and safety of a nebulizing suspension of budesonide (containing 0.25 mg, 0.5 mg, or 1.0 mg of budesonide per dose), administered once a day, in pediatric asthmatic patients aged six months to eight years.

Methodology

This was a multicenter, randomized double-blind, placebo-controlled, parallel-group study.

Number of Subjects

The total number of patients in the study was 359, the number analyzed for efficacy was 358 and the number analyzed for safety was 359.

Diagnoses and Main Criteria for Inclusion

Patients were asthmatic children who had not been treated with steroids in the 30 days prior to initiation of the study treatment. They were aged six months to eight years of age and had a diagnosis of asthma as defined by the National Institutes of Health of the U.S. Department of Health and Human Services, including: (a) exacerbations of cough and/or wheezing on a frequent basis, including nocturnal asthma, with infrequent severe exacerbations during the last six months; (b) daily use of at least one chronic asthma medication with periodic use of breakthrough medication for at least three months prior to Visit 1; (c) basal FEV_1 (forced expiratory volume, in liters per second) of ≧50% of predicted, and reversibility of ≧15% at 15±5 minutes after a standard dose of inhaled bronchodilator for patients old enough to perform consistent pulmonary function tests (PFT).

Test Drug, Doses, and Mode of Administration

Budesonide was administered once per day as a nebulized suspension, at 0.25 mg, 0.5 mg, or 1.0 mg per

administration, via a Pari LC-Jet Plus® nebulizer connected to a Pari Master® compressor (Pari Respiratory Equipment, Inc., Richmond, Va.) with a face mask or a mouth piece. The placebo was the solvent used for the budesonide suspension (0.1 mg disodium edetate, 8.5 mg NaCl, 0.2 mg polysorbate, 0.28 mg anhydrous citric acid, and 0.5 mg sodium citrate per 1 ml water) but without budesonide.

Efficacy Variables

Primary efficacy variables were mean changes from baseline in daytime and nighttime asthma symptom scores over the 12 week treatment phase. The symptom scores are based on the subjective evaluation by the patients or their parents based on a 0–3 rating system in which 0=no symptoms, 1=mild symptoms, 2=moderate symptoms, and 3=severe symptoms.

Secondary efficacy variables were: (a) patient outcomes, including the proportion of patients who were discontinued from the study for any reason and the proportion of patients who were discontinued from this study due to worsening asthma; (b) the number of days breakthrough (bronchodilator) medication was used; (c) spirometry test variables, including FEV_1, FEF_{25-75} (forced expiratory flow during the middle half of the forced vital capacity in liters per second) and FVC (forced vital capacity in liters), performed at clinic visits in the subset of patients capable of performing spirometry testing; (d) PEF (peak expiratory flow in liters per minute) measured daily in the morning and evening in the subset of patients capable of performing PEF testing; (e) changes in health status measurements, including the Modified Functional Status II Scale Child Health Status Scale and the RAND General Health Index; and (f) differences in asthma-related health care utilization and indirect health care costs.

Safety Variables

Safety variables were: (a) reported adverse effects that could be due to the drug; (b) morning basal and post-ACTH-simulation effects on plasma cortisol levels (HPA-axis function); and (c) changes in physical examinations, vital signs, and clinical laboratory tests, including oropharyngeal and nasal fungal cultures.

Statistical Methods

Analysis of variance was used to compare differences between treatment groups for all efficacy variables, with the exception of patient outcomes, which were analyzed using Fisher's exact test. Analysis of variance was also used for morning basal and post-ACTH-simulation effects on plasma cortisol levels. Descriptive statistics were used to present all other safety data.

Efficacy Results

Results of nighttime and daytime asthma symptom scores, and the number of days of use of breakthrough medication are presented in Table 1. Data are expressed as the adjusted mean change from baseline over the 12-week treatment phase, all patients treated, last value carried forward (*p≦0.050, **p≦0.010, and ***p≦0.001 versus placebo (PBO); "n" is number of patients). Thus improvements are indicated by negative values of these variables. Patients in the 0.25 mg, 0.5 mg, and 1.0 mg per day treatment groups showed statistically significant improvements in their asthma symptom scores and fewer days of bronchodilator therapy when compared to placebo.

The total proportion of patients who were discontinued from the placebo group (28%) was greater than that for the budesonide groups (19%, 24%, and 14% for the 0.25 mg, 0.5 mg and 1.0 mg groups, respectively); the proportion in the placebo group was significantly different from that in the 1 mg group (p=0.020). The proportion of patients in the placebo group discontinuing due to worsening asthma (23%) was also greater than for the budesonide groups (14%, 17% and 13% of patients in the 0.25 mg, 0.5 mg and 1.0 mg groups, respectively). These differences were not statistically significant. Since the study was double-blind, patients with worsening asthma in all study groups were discontinued in order to ensure that the placebo patients with worsening asthma could receive alternate therapy.

TABLE 1

Comparison of the Efficacy of Three Different Doses of Budesonide

		Budesonide Dose		
Variable	PBO (n = 92)	0.25 mg (n = 91)	0.5 mg (n = 82)	1.0 mg (n = 93)
Asthma scores:				
Nighttime	−0.16	−0.49***	−0.42**	−0.42**
Daytime	−0.26	−0.57**	−0.46*	−0.50*
Days of use of bronchodilator	−4.19	−6.26	−5.31*	−5.98*
FEV (L)	−0.07 (n = 38)	−0.01 (n = 29)	0.03* (n = 28)	0.03* (n = 33)
Morning PEF (L/min)	7.1 (n = 55)	14.4 (n = 44)	6.5 (n = 41)	10.9 (n = 55)

Improvements in lung function were associated with budesonide treatment in the subset of patients capable of performing PFT (Table 1). Clinically and statistically significant improvements in FEV_1 were observed in the 0.5 mg and 1.0 mg budesonide treatment groups compared to placebo. Improvements in FVC, FEF_{25-75} and morning and evening PEF were also observed in the budesonide groups, with FVC improvements in the 0.5 mg treatment group being statistically significant compared to placebo.

Patients in the 0.25 mg budesonide treatment group had clinically and statistically significant improvements compared to placebo in health status scores at weeks 4 and 12 for the FS-II(R) General score. Improvements were also seen in the FS-II(R) Specific scores, with statistical significance compared to placebo for the 0.5 mg budesonide group at week 12. Patients in all the budesonide treatment groups also demonstrated improvements in the RAND General Health Index scores compared to placebo. In addition, patients in the budesonide treatment groups showed improvements in health care utilization and fewer asthma-related phone calls to physicians. Variables associated with indirect costs, including days absent from school, and days in which routine was interrupted also showed improvement.

Safety Results

There were no deaths reported during the study. There were a total of 10 serious adverse events in 8 of the patients in the study. There were 4 discontinuations due to adverse events.

This study showed that children aged between six months and eight years with asthma, receiving budesonide at the three doses once a day for 12 weeks, had no clinically relevant differences in the frequency of clinically significant changes in nasal or oral fungal cultures between treatment groups. There were no clinically relevant differences between treatment groups in vital signs or physical examination differences.

Assessments to determine the possible effects of study treatment on basal and post-ACTH-stimulated plasma cortisol levels showed no significant differences between active treatment groups and placebo from baseline to week 12. Thus, there was no evidence of HPA-axis suppression by

budesonide at the three doses studied. ACTH production is stimulated by injection (intravenous for young children and intramuscular for infants) of corticotropin one hour before morning blood sampling.

Conclusion

This study in infants and young children aged six months to eight years with asthma demonstrated that the budesonide containing suspension significantly improved both nighttime and daytime asthma symptoms compared to placebo. Efficacy was further supported by a decrease in the use of short-acting bronchodilators and by an increase in FEV_1 (in the subgroup of patients who could consistently perform spirometry). Furthermore, there were no differences between treatments in spontaneously reported adverse events or response to ACTH-stimulation tests, strongly supporting the safety of 0.25 mg to 1.0 mg budesonide containing suspension administered once per day. All three doses of budesonide in suspension were more efficacious than placebo, but there were no differences between the three active treatments.

In summary, budesonide in a nebulized suspension, administered at 0.25 mg, 0.5 mg, or 1.0 mg once daily, is an effective and well-tolerated treatment for non-steroid-treated infants and young children between six months and eight years of age.

Example 2

A Phase III Study of Four Dose Regimens of Budesonide in a Nebulizing Suspension and Placebo in Asthmatic Children Aged Eight Years and Younger

Objectives

The objectives of the study were to compare the relative efficacy and safety of budesonide in a nebulizing suspension (0.25 mg administered once a day (QD), 0.25 mg administered twice per day (BID), 0.5 mg BID or 1.0 mg QD) in pediatric asthmatic patients aged six months to eight years.

Methodology

This was a multicenter, randomized double-blind, placebo-controlled, parallel-group study.

Number of Subjects

The number of patients in the study was 481, the number analyzed for efficacy was 471, and the number analyzed for safety was 480.

Diagnoses and Main Criteria for Inclusion

Patients were mild to moderate asthmatic children aged six months to eight years of age with a diagnosis of asthma as defined by the National Institutes of Health of the U.S. Department of Health and Human Services, including: (a) exacerbations of cough and/or wheezing on a frequent basis, including nocturnal asthma, with infrequent severe exacerbations during the last six months; (b) daily use of at least one chronic asthma medication (which could have been an inhaled GCS) with periodic use of breakthrough medication for at least three months prior to Visit 1; and (c) basal FEV_1 of ≧50% of predicted and reversibility of ≧15% at 15±5 minutes after a standard dose of inhaled bronchodilator for patients capable of performing consistent PFTs.

Test Drug, Doses and Mode of Administration

Budesonide was administered once per day as a nebulized suspension, at the indicated doses (0.25 mg QD, 0.25 mg BID, 0.5 mg BID or 1.0 mg QD) by the mode described in Example 1.

Efficacy Variables

Primary efficacy variables were mean changes from baseline in daytime and nighttime asthma symptom scores over the 12-week treatment phase. The symptom scores were obtained as in Example 1.

Secondary efficacy variables were: (a) the number of days breakthrough (bronchodilator) medication was used; (b) spirometry test variables, including FEV_1, FEF_{25-75}, and FVC performed at clinic visits in the subset of patients capable of performing spirometry testing; (c) PEF measured daily in the morning and evening in the subset of patients capable of performing PEFs; and (d) proportion of patient discontinuations from the study.

Safety Variables

Safety variables were: (a) reported adverse events that could be due to the drug; (b) morning basal and post-ACTH-simulation effects on plasma cortisol levels (HPA-axis function) in a subset of patients; and (c) changes in physical examinations, vital signs and clinical laboratory tests, including oropharyngeal and nasal fungal cultures.

Statistical Methods

Analysis of variance was used to compare differences between treatment groups for all efficacy variables, with the exception of patient discontinuations from the study, which was analyzed using Fisher's exact test. Analysis of variance was also used for morning basal and post-ACTH-simulation effects on plasma cortisol levels. Descriptive statistics were used to present all other safety data.

Efficacy Results

A total of 481 patients were included in the study. Patient demographies were similar for the four treatment groups. Males constituted 64.4% of the randomized patients. 80.5% of the patients were Caucasian, with the rest being Blacks (13.7%), Hispanics (3.7%), and other ethnic groups (2.1%). The mean age, weight, and height at screening were 55±26.3 months (range 7–108 months), 43.1±16.3 pounds (19.5±7.4 kg) and 106.5±16.4 cm, respectively. The mean duration of asthma at screening was 34.2±22.9 months. The mean nighttime and daytime asthma symptom scores at baseline were 1.22±0.62 and 1.28±0.50, respectively. A total of 164 (34.1%) of the patients were capable of performing PEF maneuvers. The mean morning and evening PEF values at baseline for these patients wee 159.9±43.0 and 168.3±43.1 L/min, respectively.

A total of 471 patients were evaluated for efficacy (all patients treated). Efficacy results are shown in Table 2. Data are expressed as the adjusted mean change from baseline over the 12-week treatment phase, all patients treated, last value carried forward (*p≦0.050; **p≦0.010 and ***p≦0.001, versus placebo; "n" is the number of patients).

TABLE 2

COMPARISON OF THE EFFICACY OF BUDESONIDE ADMINISTERED ONCE AND TWICE PER DAY

		Budesonide Dose			
	Placebo	0.25 mg QD	0.25 mg BID	0.5 mg BID	1.0 mg QD
Nighttime Asthma Symptom Score	−0.13 (n = 92)	−0.28 (n = 93)	−0.49*** (n = 97)	−0.42** (n = 96)	−0.40** (n = 93)
Daytime Asthma Symptom Score	−0.19 (n = 92)	−0.28 (n = 92)	−0.40* (n = 97)	−0.46** (n = 96)	−0.37* (n = 93)
Number of Days Use of Breakthrough Medication	−2.36 (n = 92)	−4.39* (n = 93)	−5.22*** (n = 97)	−4.92** (n = 96)	−4.38* (n = 93)
Morning PEF	−0.2 (n = 32)	10.9 (n = 32)	23.0** (n = 34)	24.8** (n = 29)	17.1* (n = 34)
Evening PEF	1.9 (n = 32)	16.8* (n = 32)	19.2* (n = 34)	21.0** (n = 29)	14.1 (n = 34)
FEV_1	0.04 (n = 28)	0.07 (n = 31)	0.03 (n = 33)	0.17* (n = 29)	0.11 (n = 34)

The data demonstrated that 0.25 mg BID, 0.5 mg BID, and 1.0 mg QD budesonide provided statistically significant and clinically relevant improvement in patient nighttime and daytime asthma symptoms compared to placebo.

Furthermore, patients receiving all four budesonide regimens had statistically significant and clinically relevant decreases in the number of days of breakthrough medication use compared to placebo.

In those children who could perform PEF assessments, statistically significant improvements in morning PEF from baseline to weeks 0–12 were seen in the 0.25 mg BID, 0.5 mg BID, and 1.0 mg QD mg budesonide treatment groups compared to placebo. Statistically significant improvements in evening PEF from baseline to weeks 0–12 were seen in the 0.25 mg QD, 0.25 mg BID, and 0.5 mg QD budesonide nebulizing suspension treatment groups compared to placebo. In those patients able to perform PFTs consistently, the lung function measures of FEV_1, FVC, and FEF_{25-75} improved clinically for all the budesonide treatment groups compared to placebo, with statistical significance achieved in FEV_1 and FVC for the budesonide 0.5 mg BID treatment group.

The total proportion of patients who were discontinued from the placebo group (39%) was greater than that for the budesonide treatment groups (21%, 21%, 19% and 31% for the 0.25 mg QD, 0.25 mg BID, 0.5 mg BID and 1.0 mg QD groups, respectively); the proportion in the placebo group was significantly different from those in the 0.25 mg QD, 0.25 mg BID, and 0.5 mg BID budesonide treatment groups ($p<0.01$). The proportion of patients in the placebo group discontinuing due to worsening asthma (26.3%) was also greater than for budesonide treatment groups (16.0%, 13.1%, 15.3% and 21.1% of patients for the 0.25 mg QD, 0.25 mg BID, 0.5 mg BID, and 1.0 mg QD groups, respectively; these differences were statistically significant for the 0.25 mg BID budesonide versus placebo comparison, $p=0.029$).

Safety Results

One randomized patient never took the study drug and therefore was not included in the safety analysis. There were no deaths reported during the study. A total of 13 serious adverse events in 13 patients were reported during the treatment phase, all recovering completely without sequelae (4, 4, 2, 1, and 4 serious adverse events in the placebo, 0.25 mg QD, 0.25 mg BID, 0.5 mg BID, and 1.0 mg QD groups, respectively). A total of six patients were discontinued due to adverse effects (2, 1, 1, and 2 patients in the placebo and the 0.25 mg BID, 0.5 mg BID, and 1.0 mg QD groups, respectively). One of the adverse events leading to discontinuation from the treatment phase was judged by the investigator to be of probable relationship to the study treatment. The patient was in the 1.0 mg QD group and developed laryngismus.

The study showed that children aged six months to eight years with asthma, receiving budesonide as a nebulized suspension at 0.25 mg QD, 0.25 mg BID, 0.5 mg BID, or 1.0 mg QD for 12 weeks had no clinically relevant differences in the type, incidence or severity of adverse events compared to placebo. There were also no apparent differences in the number of patients with clinically significant changes in nasal or oral fungal cultures between treatment groups. There were no clinically relevant differences between treatment groups in vital signs or physical examination outcomes.

Assessments to determine the possible effects of study treatment on basal and post-ACTH-stimulated plasma cortisol levels showed no significant differences between the active treatment groups and placebo from baseline to week 12. Thus, there was no evidence of HPA-axis suppression by budesonide in a nebulized suspension when administered in the four regimens studied.

Conclusion

Budesonide in a nebulized suspension, when administered in regimens of 0.25 mg QD, 0.25 mg BID, 0.5 mg BID, or 1.0 mg QD, was effective and well tolerated by infants and young children aged between six months and eight years with asthma who had previously been or not been treated with inhaled GCS.

Other Embodiments

It is understood that while the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

What is claimed is:

1. A method of treating a patient suffering from a respiratory disease, the method comprising administering to the patient a nebulized dose of a budesonide composition in a continuing regimen at a frequency of not more than once per day.

2. The method of claim **1**, wherein the frequency is once and only once per day.

3. The method of claim **2**, wherein budesonide is the only active ingredient in the budesonide composition.

4. The method of claim **1**, wherein the frequency is once and only once every other day.

5. The method of claim **4**, wherein budesonide is the only active ingredient in the budesonide composition.

6. The method of claim **1**, wherein the respiratory disease is selected from the group consisting of an inflammatory airway disease, croup, and bronchopulmonary dysplasia.

7. The method of claim **6**, wherein the respiratory disease is asthma.

8. The method of claim **7**, wherein budesonide is the only active ingredient in the budesonide composition.

9. The method of claim **6**, wherein the respiratory disease is chronic obstructive pulmonary disease or bronchiolitis.

10. The method of claim **9**, wherein budesonide is the only active ingredient in the budesonide composition.

11. The method of claim **6**, wherein budesonide is the only active ingredient in the budesonide composition.

12. The method of claim **1**, wherein the patient is one day to fifteen years old.

13. The method of claim **12**, wherein budesonide is the only active ingredient in the budesonide composition.

14. The method of claim **1**, wherein the patient is one month to eight years old.

15. The method of claim **14**, wherein budesonide is the only active ingredient in the budesonide composition.

16. The method of claim **1**, wherein the patient is six months to five years old.

17. The method of claim **16**, wherein budesonide is the only active ingredient in the budesonide composition.

18. The method of claim **1**, wherein the budesonide composition contains 0.05 mg to 15 mg budesonide.

19. The method of claim **18**, wherein the budesonide composition further comprises water and 0.05 mg to 0.15 mg sodium edetate, 8.0 mg to 9.0 mg sodium chloride, 0.15 mg to 0.25 mg polysorbate, 0.25 mg to 0.30 mg anhydrous citric acid, and 0.45 mg to 0.55 mg sodium citrate per 1 ml of water.

20. The method of claim **19**, wherein budesonide is the only active ingredient in the budesonide composition.

21. The method of claim **18**, wherein budesonide is the only active ingredient in the budesonide composition.

22. The method of claim **1**, wherein the budesonide composition contains 0.1 mg to 2.0 mg budesonide.

23. The method of claim **22**, wherein budesonide is the only active ingredient in the budesonide composition.

24. The method of claim **1**, wherein the budesonide composition contains 0.25 mg to 1.0 mg budesonide.

25. The method of claim **24**, wherein budesonide is the only active ingredient in the budesonide composition.

26. The method of claim **1**, wherein the budesonide composition is a suspension.

27. The method of claim **26**, wherein budesonide is the only active ingredient in the budesonide composition.

28. The method of claim **1**, wherein budesonide is the only active ingredient in the budesonide composition.

29. A kit for treating respiratory diseases, the kit comprising (a) a budesonide composition in a sealed container, the composition containing 0.05 mg to 15 mg budesonide and a solvent, and (b) a label indicating administration by nebulization in a continuing regimen at a frequency of not more than once per day.

30. The kit of claim **29**, wherein budesonide is the sole active ingredient in the composition.

* * * * *

EXHIBIT B

US006899099B2

(12) **United States Patent**
Andersson et al.

(10) **Patent No.: US 6,899,099 B2**
(45) **Date of Patent: *May 31, 2005**

(54) **METHOD FOR TREATING A RESPIRATORY DISEASE**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 101 days.

This patent is subject to a terminal disclaimer.

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(63) Continuation of application No. 09/220,137, filed on Dec. 23, 1998, now Pat. No. 6,598,603.
(60) Provisional application No. 60/070,291, filed on Dec. 31, 1997.

(51) **Int. Cl.**[7] **A61M 11/00**
(52) **U.S. Cl.** **128/200.14**; 128/203.12
(58) **Field of Search** 128/200.14, 200.23, 128/203.12, 203.15

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(57) **ABSTRACT**

The invention provides a novel method of treating respiratory diseases, e.g., pediatric asthma, in a continuing regimen with not more than one daily dose of the drug budesonide using a nebulizer.

27 Claims, No Drawings

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METHOD FOR TREATING A RESPIRATORY DISEASE

This application in a continuation of U.S. application Ser. No. 09/220,137, filed Dec. 23, 1998, now U.S. Pat. No. 6,598,603, which claims benefit of U.S. Provisional Application Ser. No. 60/070,291, filed Dec. 31, 1997. The disclosures of U.S. application Ser. No. 09/220,137 and U.S. Provisional Application No. 60/070,291 are incorporated herein by reference in their entirety.

BACKGROUND OF THE INVENTION

The invention relates to the treatment of respiratory diseases.

There is significant difficulty in the treatment of young children, including infants, who suffer from respiratory diseases, e.g., asthma. In light of the requirement for frequent and repeated administration of appropriate drugs, issues of compliance and convenience are major aspects of this problem. Furthermore, current methods of intrapulmonary delivery of drugs, e.g., glucocorticosteroids (GCS), are not optimal for use in infants and young children.

SUMMARY OF THE INVENTION

The invention provides a new method of treating respiratory diseases such as asthma that involves administering a budesonide composition with a nebulizer not more than once per day. This administration regimen improves compliance and convenience, both significant factors in treating these diseases, particularly in infants and young children. Moreover, the nebulizer is readily and effectively used with infants as well as young children.

Specifically, the invention features a method of treating a patient suffering from a respiratory disease in which a composition, e.g., a suspension, of budesonide is administered by nebulization at a frequency of between once per day and once per month in a continuing regimen. For example, the frequency of administration can be once and only once per day, or once and only once every two days. The doses can be, e.g., 0.05 mg to 15 mg, 0.1 mg to 2.0 mg, or 0.25 mg to 1.0 mg budesonide. The drug can be provided as an aqueous suspension in which the budesonide is suspended in a solvent containing about 0.05 mg to 0.15 mg sodium edetate, about 8.0 mg to 9.0 mg sodium chloride, about 0.15 mg to 0.25 mg polysorbate, about 0.25 mg to 0.30 mg anhydrous citric acid, and about 0.45 mg to 0.55 mg sodium citrate per 1 ml of water.

This new method of treatment can be used in patients suffering from respiratory diseases that include, for example, inflammatory airway diseases, croup, and bronchopulmonary dysplasia. Inflammatory airway diseases include asthma, chronic obstructive pulmonary disease (COPD), and bronchiolitis. Patients can be any age from birth, e.g., newborn, one day to fifteen years old, one month to eight years old, or six months to five years old. The method is also effective in older patients.

A "continuing regimen," is a treatment regimen of a series of two or more administrations that occur over days, weeks, months, or years. The dosage of each administration can be the same or varied throughout the continuing regimen.

The doses of budesonide specified for administration by nebulization are those added to the nebulizing device. In a typical situation, approximately 40% to 60% of the drug actually leaves the nebulizer, and of this only approximately 25% (i.e., 10% to 15% of the nominal dose) is delivered to the patient. This is because the drug is delivered constantly, and when the patient is exhaling, the drug leaving the nebulizer will not be delivered to the patient; it will instead be lost to the environment. Of the amount delivered to the patient, approximately 6% to 9% of the nominal dose is delivered to the lungs.

The invention also features a kit for treating respiratory diseases, the kit including a budesonide composition in a sealed container, the composition including 0.05 mg to 15 mg budesonide and a solvent, and a label indicating administration by nebulization in a continuing regimen at a frequency of not more than once per day.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. All publications, patent applications, patents and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

Other features and advantages of the invention, e.g., treatment of childhood asthma, will be apparent from the following description and from the claims.

DETAILED DESCRIPTION

The invention is a convenient yet highly effective method of treating asthma involving not more than one administration per day in a continuing dosage regimen. This new method represents a significant advantage, particularly in infants and young children in which it is frequently difficult to achieve compliance with treatments involving more frequent administrations. Such treatments can involve the use of portable propellant-based inhalers which a young child can either use improperly, lose, or be embarrassed to use in front of his or her peers. Once a day or less frequent treatments are cost effective and result in an improved quality of life. In general, a patient (or a patient's family) can choose a time of administration that is convenient for them.

In infants, standard inhalation devices are technically difficult to use. The fact that in the new method the drug can be delivered by a mask applied over the infant's nose and mouth obviates this problem. In addition, in using the nebulizer for administration, the drug is constantly pumped into the face mask. Thus, effective drug delivery does not require constant and deep inhalation. This aspect of the treatment is also advantageous in, for example, incapacitated or neurologically impaired patients.

Two randomized, double-blind, placebo-controlled, twelve-week studies assessed the efficacy and safety of budesonide in children six months to eight years of age who had persistent asthma that was not effectively controlled by non-GCS therapies. The budesonide suspended in a solvent (or a placebo) was administered once per day by a nebulizer connected to a compressor. This treatment resulted in statistically significant improvements in asthma symptoms and a decrease in the number of days in which auxiliary bronchodilator medication was used. Furthermore, there were no significant differences between treatment groups in the type, incidence, or severity of adverse events. There were also no apparent differences between the groups in changes observed in physical examinations, clinical laboratory tests, or oropharyngeal or nasal fungal cultures. Measurement of

adrenocorticotropic hormone (ACTH)-induced plasma cortisol levels showed no evidence of hypothalamus-pituitary-adrenal (HPA)-axis suppression by budesonide after twelve weeks of treatment. In summary, these results demonstrated both the efficacy and safety of budesonide when administered to children once per day.

After it has been taken up by airway cells, budesonide forms conjugates (esters) with long-chain fatty acids such as oleic acid. Unlike free budesonide, the budesonide conjugates are inactive as they do not bind to the GCS receptor. However, the conjugation of budesonide is a reversible process. As the concentration of free budesonide in the airway cells falls, the conjugates undergo lipolysis, and further free budesonide is produced, thus maintaining the level available for receptor binding. Intracellular conjugated budesonide thus acts as a "depot" of free budesonide in the airway cells, prolonging the local effect of the compound. This proposed mechanism of action is exemplary; the invention is not limited by any particular mechanism of action.

Methods of Treating Respiratory Diseases

The invention features a new method for treating a patient suffering from a respiratory disease using the drug budesonide which is administered to the patient not more frequently than once per day. It can be delivered, for example, once a day, once every 1.5 days, once every 2 days, once every 3 days, once a week, once every two weeks, or once a month. Treatment is in a continuing regimen for as long as required.

The drug can be delivered dispersed in a solvent, e.g., in the form of a solution or a suspension. It can be suspended in an appropriate physiological solution, e.g., physiological saline or a buffered solution containing 0.05 mg to 0.15 mg disodium edetate, 8.0 mg to 9.0 mg NaCl, 0.15 mg to 0.25 mg polysorbate, 0.25 mg to 0.30 mg anhydrous citric acid, and 0.45 mg to 0.55 mg sodium citrate per 1 ml of water so as to achieve a pH of about 4.0 to 5.0. The budesonide suspension can made, for example, from micronized budesonide.

The therapeutic suspensions can also contain one or more excipients. Excipients are well known in the art and include buffers (e.g., citrate buffer, phosphate buffer, acetate buffer and bicarbonate buffer), amino acids, urea, alcohols, ascorbic acid, phospholipids, proteins (e.g., serum albumin), EDTA, sodium chloride, liposomes, mannitol, sorbitol, and glycerol. Solutions or suspensions can be encapsulated in liposomes or biodegradable microspheres.

The budesonide suspension is provided in a substantially sterile form by, for example, dry-heating the budesonide powder for 2 to 6 hours at 90° C. to 150° C. and employing sterile manufacture for the rest of the process. This involves production and sterilization by filtration of the buffered solvent solution used for the suspension, aseptic suspension of the budesonide in the sterile buffered solvent solution, and dispensing of the suspension into sterile receptacles by methods familiar to those of ordinary skill in the art. This process results in a sterility assurance of 6 as required by the Food and Drug Administration of the U.S. government.

The route of administration is intrapulmonary and the drug is delivered in a nebulized composition by, for example, a nebulizer connected to a compressor (e.g., the Pari LC-Jet Plus® nebulizer connected to a Pari Master® compressor manufactured by Pari Respiratory Equipment, Inc., Richmond, Va.).

Patients are those suffering from a respiratory disease. Relevant respiratory diseases include inflammatory airway diseases, croup, and bronchopulmonary dysplasia. Examples of inflammatory airway diseases include asthma, COPD and bronchiolitis.

Patients can be of either sex. They can be treated by the new method at any age from birth. They can, for example be treated as early as thirty minutes after birth. The patients can also much older, e.g., twelve months, two years, four years, ten years, forty years, or even seventy years of age, or older. Patients can be six months to five or eight years old.

Doses of budesonide can be the same, or can be varied, for patients of all age groups and all sizes and weights. When administered as a nebulized suspension, the dose can be, e.g., 0.05 mg to 15 mg, 0.1 mg to 2.0 mg, or 0.25 mg to 1.0 mg budesonide per administration. Evening administration can result in better control of nocturnal and early morning symptoms which are frequent problems in asthma. If excess budesonide is used in a single administration, it is unlikely that harmful effects will occur.

Nebulizable budesonide is provided, for example, as single dose units (e.g., sealed plastic containers or vials) packed in foil envelopes. Each vial contains a unit dose (e.g., 0.25 mg, 0.5 mg, or 1.0 mg) of micronized budesonide suspended in a volume, e.g., 2 ml, of solvent. The unit dose or, if desired and directed by a physician, a fraction of the unit dose is added to the nebulizer. Patients should rinse out their mouths with water after administration of each dose.

Where diseases other than asthma are to be treated with solvent dispersed budesonide, optimal doses can be established by methods familiar to those in the art, e.g., methods analogous to those described in Examples 1 and 2. Doses, for example, for COPD, bronchiolitis, croup, and bronchopulmonary dysplasia, as in asthma, can generally be 0.05 to 15 mg, 0.1 mg to 2.0 mg, or 0.25 mg to 1.0 mg budesonide per administration.

The following examples are meant to illustrate, not limit, the invention.

EXAMPLES

Example 1

A Phase III Study of Three Dose Levels of Once-A-Day Budesonide Nebulizing Suspension and Placebo in Asthmatic Children

Objectives

The objectives of the study were to compare the relative efficacy and safety of a nebulizing suspension of budesonide (containing 0.25 mg, 0.5 mg, or 1.0 mg of budesonide per dose), administered once a day, in pediatric asthmatic patients aged six months to eight years.

Methodology

This was a multicenter, randomized double-blind, placebo-controlled, parallel-group study.

Number of Subjects

The total number of patients in the study was 359, the number analyzed for efficacy was 358 and the number analyzed for safety was 359.

Diagnoses and Main Criteria for Inclusion

Patients were asthmatic children who had not been treated with steroids in the 30 days prior to initiation of the study treatment. They were aged six months to eight years of age and had a diagnosis of asthma as defined by the National Institutes of Health of the U.S. Department of Health and Human Services, including: (a) exacerbations of cough and/or wheezing on a frequent basis, including nocturnal asthma, with infrequent severe exacerbations during the last six months; (b) daily use of at least one chronic asthma medication with periodic use of breakthrough medication for at least three months prior to Visit 1; (c) basal FEV_1 (forced expiratory volume, in liters per second) of ≧50% of predicted, and reversibility of ≧15% at 15±5 minutes after

a standard dose of inhaled bronchodilator for patients old enough to perform consistent pulmonary function tests (PFT).

Test Drug, Doses, and Mode of Administration

Budesonide was administered once per day as a nebulized suspension, at 0.25 mg, 0.5 mg, or 1.0 mg per administration, via a Pari LC-Jet Plus® nebulizer connected to a Pari Master® compressor (Pari Respiratory Equipment, Inc., Richmond, Va.) with a face mask or a mouth piece. The placebo was the solvent used for the budesonide suspension (0.1 mg disodium edetate, 8.5 mg NaCl, 0.2 mg polysorbate, 0.28 mg anhydrous citric acid, and 0.5 mg sodium citrate per 1 ml water) but without budesonide.

Efficacy Variables

Primary efficacy variables were mean changes from baseline in daytime and nighttime asthma symptom scores over the 12 week treatment phase. The symptom scores are based on the subjective evaluation by the patients or their parents based on a 0–3 rating system in which 0=no symptoms, 1=mild symptoms, 2=moderate symptoms, and 3=severe symptoms.

Secondary efficacy variables were: (a) patient outcomes, including the proportion of patients who were discontinued from the study for any reason and the proportion of patients who were discontinued from this study due to worsening asthma; (b) the number of days breakthrough (bronchodilator) medication was used; (c) spirometry test variables, including FEV_1, FEF_{25-75} (forced expiratory flow during the middle half of the forced vital capacity in liters per second) and FVC (forced vital capacity in liters), performed at clinic visits in the subset of patients capable of performing spirometry testing; (d) PEF (peak expiratory flow in liters per minute) measured daily in the morning and evening in the subset of patients capable of performing PEF testing; (e) changes in health status measurements, including the Modified Functional Status II Scale Child Health Status Scale and the RAND General Health Index; and (f) differences in asthma-related health care utilization and indirect health care costs.

Safety Variables

Safety variables were: (a) reported adverse effects that could be due to the drug; (b) morning basal and post-ACTH-simulation effects on plasma cortisol levels (HPA-axis function); and (c) changes in physical examinations, vital signs, and clinical laboratory tests, including oropharyngeal and nasal fungal cultures.

Statistical Methods

Analysis of variance was used to compare differences between treatment groups for all efficacy variables, with the exception of patient outcomes, which were analyzed using Fisher's exact test. Analysis of variance was also used for morning basal and post-ACTH-simulation effects on plasma cortisol levels. Descriptive statistics were used to present all other safety data.

Efficacy Results

Results of nighttime and daytime asthma symptom scores, and the number of days of use of breakthrough medication are presented in Table 1. Data are expressed as the adjusted mean change from baseline over the 12-week treatment phase, all patients treated, last value carried forward (*p≦0.050, **p≦0.010, and ***p≦0.001 versus placebo (PBO); "n" is number of patients). Thus improvements are indicated by negative values of these variables. Patients in the 0.25 mg, 0.5 mg, and 1.0 mg per day treatment groups showed statistically significant improvements in their asthma symptom scores and fewer days of bronchodilator therapy when compared to placebo.

The total proportion of patients who were discontinued from the placebo group (28%) was greater than that for the budesonide groups (19%, 24%, and 14% for the 0.25 mg, 0.5 mg and 1.0 mg groups, respectively); the proportion in the placebo group was significantly different from that in the 1 mg group (p=0.020). The proportion of patients in the placebo group discontinuing due to worsening asthma (23%) was also greater than for the budesonide groups (14%, 17% and 13% of patients in the 0.25 mg, 0.5 mg and 1.0 mg groups, respectively). These differences were not statistically significant. Since the study was double-blind, patients with worsening asthma in all study groups were discontinued in order to ensure that the placebo patients with worsening asthma could receive alternate therapy.

TABLE 1

Comparison of the Efficacy of Three Different Doses of Budesonide

		Budesonide Dose		
Variable Asthma scores:	PBO (n = 92)	0.25 mg (n = 91)	0.5 mg (n = 82)	1.0 mg (n = 93)
Nighttime	−0.16	−0.49***	−0.42**	−0.42**
Daytime	−0.26	−0.57**	−0.46*	−0.50*
Days of use of bronchodilator	−4.19	−6.26*	−5.31*	−5.98*
FEV_1 (L)	−0.07 (n = 38)	−0.01 (n = 29)	0.03* (n = 28)	0.03* (n = 33)
Morning PEF (L/min)	7.1 (n = 55)	14.4 (n = 44)	6.5 (n = 41)	10.9 (n = 55)

Improvements in lung function were associated with budesonide treatment in the subset of patients capable of performing PFT (Table 1). Clinically and statistically significant improvements in FEV_1 were observed in the 0.5 mg and 1.0 mg budesonide treatment groups compared to placebo. Improvements in FVC, FEF_{25-75} and morning and evening PEF were also observed in the budesonide groups, with FVC improvements in the 0.5 mg treatment group being statistically significant compared to placebo.

Patients in the 0.25 mg budesonide treatment group had clinically and statistically significant improvements compared to placebo in health status scores at weeks 4 and 12 for the FS-II(R) General score. Improvements were also seen in the FS-II(R) Specific scores, with statistical significance compared to placebo for the 0.5 mg budesonide group at week 12. Patients in all the budesonide treatment groups also demonstrated improvements in the RAND General Health Index scores compared to placebo. In addition, patients in the budesonide treatment groups showed improvements in health care utilization and fewer asthma-related phone calls to physicians. Variables associated with indirect costs, including days absent from school, and days in which routine was interrupted also showed improvement.

Safety Results

There were no deaths reported during the study. There were a total of 10 serious adverse events in 8 of the patients in the study. There were 4 discontinuations due to adverse events.

This study showed that children aged between six months and eight years with asthma, receiving budesonide at the three doses once a day for 12 weeks, had no clinically relevant differences in the frequency of clinically significant changes in nasal or oral fungal cultures between treatment groups. There were no clinically relevant differences between treatment groups in vital signs or physical examination differences.

Assessments to determine the possible effects of study treatment on basal and post-ACTH-stimulated plasma cor-

tisol levels showed no significant differences between active treatment groups and placebo from baseline to week 12. Thus, there was no evidence of HPA-axis suppression by budesonide at the three doses studied. ACTH production is stimulated by injection (intravenous for young children and intramuscular for infants) of corticotropin one hour before morning blood sampling.

Conclusion

This study in infants and young children aged six months to eight years with asthma demonstrated that the budesonide containing suspension significantly improved both nighttime and daytime asthma symptoms compared to placebo. Efficacy was further supported by a decrease in the use of short-acting bronchodilators and by an increase in FEV_1 (in the subgroup of patients who could consistently perform spirometry). Furthermore, there were no differences between treatments in spontaneously reported adverse events or response to ACTH-stimulation tests, strongly supporting the safety of 0.25 mg to 1.0 mg budesonide containing suspension administered once per day. All three doses of budesonide in suspension were more efficacious than placebo, but there were no differences between the three active treatments.

In summary, budesonide in a nebulized suspension, administered at 0.25 mg, 0.5 mg, or 1.0 mg once daily, is an effective and well-tolerated treatment for non-steroid-treated infants and young children between six months and eight years of age.

Example 2

A Phase III Study of Four Dose Regimens of Budesonide in a Nebulizing Suspension and Placebo in Asthmatic Children Aged Eight Years and Younger

Objectives

The objectives of the study were to compare the relative efficacy and safety of budesonide in a nebulizing suspension (0.25 mg administered once a day (QD), 0.25 mg administered twice per day (BID), 0.5 mg BID or 1.0 mg QD) in pediatric asthmatic patients aged six months to eight years.

Methodology

This was a multicenter, randomized double-blind, placebo-controlled, parallel-group study.

Number of Subjects

The number of patients in the study was 481, the number analyzed for efficacy was 471, and the number analyzed for safety was 480.

Diagnoses and Main Criteria for Inclusion

Patients were mild to moderate asthmatic children aged six months to eight years of age with a diagnosis of asthma as defined by the National Institutes of Health of the U.S. Department of Health and Human Services, including: (a) exacerbations of cough and/or wheezing on a frequent basis, including nocturnal asthma, with infrequent severe exacerbations during the last six months; (b) daily use of at least one chronic asthma medication (which could have been an inhaled GCS) with periodic use of breakthrough medication for at least three months prior to Visit 1; and (c) basal FEV_1 of ≧50% of predicted and reversibility of ≧15% at 15±5 minutes after a standard dose of inhaled bronchodilator for patients capable of performing consistent PFTs.

Test Drug, Doses and Mode of Administration

Budesonide was administered once per day as a nebulized suspension, at the indicated doses (0.25 mg QD, 0.25 mg BID, 0.5 mg BID or 1.0 mg QD) by the mode described in Example 1.

Efficacy Variables

Primary efficacy variables were mean changes from baseline in daytime and nighttime asthma symptom scores over the 12-week treatment phase. The symptom scores were obtained as in Example 1.

Secondary efficacy variables were: (a) the number of days breakthrough (bronchodilator) medication was used; (b) spirometry test variables, including FEV_1, FEF_{25-75}, and FVC performed at clinic visits in the subset of patients capable of performing spirometry testing; (c) PEF measured daily in the morning and evening in the subset of patients capable of performing PEFs; and (d) proportion of patient discontinuations from the study.

Safety Variables

Safety variables were: (a) reported adverse events that could be due to the drug; (b) morning basal and post-ACTH-simulation effects on plasma cortisol levels (HPA-axis function) in a subset of patients; and (c) changes in physical examinations, vital signs and clinical laboratory tests, including oropharyngeal and nasal fungal cultures.

Statistical Methods

Analysis of variance was used to compare differences between treatment groups for all efficacy variables, with the exception of patient discontinuations from the study, which was analyzed using Fisher's exact test. Analysis of variance was also used for morning basal and post-ACTH-simulation effects on plasma cortisol levels. Descriptive statistics were used to present all other safety data.

Efficacy Results

A total of 481 patients were included in the study. Patient demographies were similar for the four treatment groups. Males constituted 64.4% of the randomized patients. 80.5% of the patients were Caucasian, with the rest being Blacks (13.7%), Hispanics (3.7%), and other ethnic groups (2.1%). The mean age, weight, and height at screening were 55±26.3 months (range 7–108 months), 43.1±16.3 pounds (19.5±7.4 kg) and 106.5±16.4 cm, respectively. The mean duration of asthma at screening was 34.2±22.9 months. The mean nighttime and daytime asthma symptom scores at baseline were 1.22±0.62 and 1.28±0.50, respectively. A total of 164 (34.1%) of the patients were capable of performing PEF maneuvers. The mean morning and evening PEF values at baseline for these patients were 159.9±43.0 and 168.3±43.1 L/min, respectively.

A total of 471 patients were evaluated for efficacy (all patients treated). Efficacy results are shown in Table 2. Data are expressed as the adjusted mean change from baseline over the 12-week treatment phase, all patients treated, last value carried forward (*p≦0.050; **p≦0.010 and ***p≦0.001, versus placebo; "n" is the number of patients).

TABLE 2

COMPARISON OF THE EFFICACY OF BUDESONIDE ADMINISTERED ONCE AND TWICE PER DAY

		Budesonide Dose			
	Placebo	0.25 mg QD	0.25 mg BID	0.5 mg BID	1.0 mg QD
Nighttime Asthma Symptom Score	−0.13 (n = 92)	−0.28 (n = 93)	−0.49*** (n = 97)	−0.42** (n = 96)	−0.40** (n = 93)
Daytime Asthma Symptom Score	−0.19 (n = 92)	−0.28 (n = 92)	−0.40* (n = 97)	−0.46** (n = 96)	−0.37* (n = 93)
Number of Days Use of Breakthrough Medication	−2.36 (n = 92)	−4.39* (n = 93)	−5.22*** (n = 97)	−4.92** (n = 96)	−4.38* (n = 93)

TABLE 2-continued

COMPARISON OF THE EFFICACY OF BUDESONIDE ADMINISTERED ONCE AND TWICE PER DAY

		Budesonide Dose			
	Placebo	0.25 mg QD	0.25 mg BID	0.5 mg BID	1.0 mg QD
Morning PEF	−0.2 (n = 32)	10.9 (n = 32)	23.0** (n = 34)	24.8** (n = 29)	17.1* (n = 34)
Evening PEF	1.9 (n = 32)	16.8* (n = 32)	19.2* (n = 34)	21.0** (n = 29)	14.1 (n = 34)
FEV_1	0.04 (n = 28)	0.07 (n = 31)	0.03 (n = 33)	0.17* (n = 29)	0.11 (n = 34)

The data demonstrated that 0.25 mg BID, 0.5 mg BID, and 1.0 mg QD budesonide provided statistically significant and clinically relevant improvement in patient nighttime and daytime asthma symptoms compared to placebo. Furthermore, patients receiving all four budesonide regimens had statistically significant and clinically relevant decreases in the number of days of breakthrough medication use compared to placebo.

In those children who could perform PEF assessments, statistically significant improvements in morning PEF from baseline to weeks 0–12 were seen in the 0.25 mg BID, 0.5 mg BID, and 1.0 mg QD mg budesonide treatment groups compared to placebo. Statistically significant improvements in evening PEF from baseline to weeks 0–12 were seen in the 0.25 mg QD, 0.25 mg BID, and 0.5 mg QD budesonide nebulizing suspension treatment groups compared to placebo. In those patients able to perform PFTs consistently, the lung function measures of FEVI, FVC, and FEF_{25-75} improved clinically for all the budesonide treatment groups compared to placebo, with statistical significance achieved in FEV_1 and FVC for the budesonide 0.5 mg BID treatment group.

The total proportion of patients who were discontinued from the placebo group (39%) was greater than that for the budesonide treatment groups (21%, 21%, 19% and 31% for the 0.25 mg QD, 0.25 mg BID, 0.5 mg BID and 1.0 mg QD groups, respectively); the proportion in the placebo group was significantly different from those in the 0.25 mg QD, 0.25 mg BID, and 0.5 mg BID budesonide treatment groups ($p<0.01$). The proportion of patients in the placebo group discontinuing due to worsening asthma (26.3%) was also greater than for budesonide treatment groups (16.0%, 13.1%, 15.3% and 21.1% of patients for the 0.25 mg QD, 0.25 mg BID, 0.5 mg BID, and 1.0 mg QD groups, respectively; these differences were statistically significant for the 0.25 mg BID budesonide versus placebo comparison, $p=0.029$).

Safety Results

One randomized patient never took the study drug and therefore was not included in the safety analysis. There were no deaths reported during the study. A total of 13 serious adverse events in 13 patients were reported during the treatment phase, all recovering completely without sequelae (4, 4, 2, 1, and 4 serious adverse events in the placebo, 0.25 mg QD, 0.25 mg BID, 0.5 mg BID, and 1.0 mg QD groups, respectively). A total of six patients were discontinued due to adverse effects (2, 1, 1, and 2 patients in the placebo and the 0.25 mg BID, 0.5 mg BID, and 1.0 mg QD groups, respectively). One of the adverse events leading to discontinuation from the treatment phase was judged by the investigator to be of probable relationship to the study treatment. The patient was in the 1.0 mg QD group and developed laryngismus.

The study showed that children aged six months to eight years with asthma, receiving budesonide as a nebulized suspension at 0.25 mg QD, 0.25 mg BID, 0.5 mg BID, or 1.0 mg QD for 12 weeks had no clinically relevant differences in the type, incidence or severity of adverse events compared to placebo. There were also no apparent differences in the number of patients with clinically significant changes in nasal or oral fungal cultures between treatment groups. There were no clinically relevant differences between treatment groups in vital signs or physical examination outcomes.

Assessments to determine the possible effects of study treatment on basal and post-ACTH-stimulated plasma cortisol levels showed no significant differences between the active treatment groups and placebo from baseline to week 12. Thus, there was no evidence of HPA-axis suppression by budesonide in a nebulized suspension when administered in the four regimens studied.

Conclusion

Budesonide in a nebulized suspension, when administered in regimens of 0.25 mg QD, 0.25 mg BID, 0.5 mg BID, or 1.0 mg QD, was effective and well tolerated by infants and young children aged between six months and eight years with asthma who had previously been or not been treated with inhaled GCS.

OTHER EMBODIMENTS

It is understood that while the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

What is claimed is:

1. A method of treating a patient suffering from a respiratory disease, the method comprising administering to the patient a nebulized dose of a budesonide composition in a continuing regimen at a frequency of not more than once per day, wherein the administration is in the evening.

2. The method of claim **1**, wherein the frequency is once and only once per day.

3. The method of claim **1**, wherein the frequency is once and only once every other day.

4. The method of claim **1**, wherein the respiratory disease is selected from the group consisting of an inflammatory airway disease, croup, and bronchopulmonary dysplasia.

5. The method of claim **4**, wherein the respiratory disease is asthma.

6. The method of claim **4**, wherein the respiratory disease is chronic obstructive pulmonary disease or bronchiolitis.

7. The method of claim **1**, wherein the patient is one day to fifteen years old.

8. The method of claim **1**, wherein the patient is one month to eight years old.

9. The method of claim **1**, wherein the patient is six months to five years old.

10. The method of claim **1**, wherein the budesonide composition contains 0.05 mg to 15 mg budesonide.

11. The method of claim **10**, wherein the budesonide composition further comprises water and 0.05 mg to 0.15 mg sodium edetate, 8.0 mg to 9.0 mg sodium chloride, 0.15 mg to 0.25 mg polysorbate, 0.25 mg to 0.30 mg anhydrous citric acid, and 0.45 mg to 0.55 mg sodium citrate per 1 ml of water.

12. The method of claim **1**, wherein the budesonide composition contains 0.1 mg to 2.0 mg budesonide.

13. The method of claim **1**, wherein the budesonide composition contains 0.25 mg to 1.0 mg budesonide.

14. The method of claim **1**, wherein the budesonide composition is a suspension.

15. The method of claim **1**, wherein the budesonide composition is a solution.

16. The method of claim **1**, wherein budesonide is the only active ingredient in the budesonide composition.

17. A kit for treating a respiratory disease, the kit comprising (a) a budesonide suspension in a sealed container, the suspension containing 0.05 mg to 15 mg budesonide and a solvent, and (b) a label indicating administration by nebulization in a continuing regimen at a frequency of not more than once per day.

18. The kit of claim **17**, wherein the frequency is once and only once per day.

19. The kit of claim **17**, wherein the frequency is once and only once every other day.

20. The kit of claim **17**, wherein the respiratory disease is selected from the group consisting of an inflammatory airway disease, croup, and bronchopulmonary dysplasia.

21. The kit of claim **20**, wherein the respiratory disease is asthma.

22. The kit of claim **20**, wherein the respiratory disease is chronic obstructive pulmonary disease or bronchiolitis.

23. The kit of claim **17**, wherein the administration is in the evening.

24. The kit of claim **17**, wherein the patient is one day to fifteen years old.

25. The kit of claim **17**, wherein the patient is one month to eight years old.

26. The kit of claim **17**, wherein the patient is six months to five years old.

27. The kit of claim **17**, wherein budesonide is the sole active ingredient in the composition.

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EXHIBIT C

(12) **United States Patent**
Karlsson et al.

(10) **Patent No.: US 7,524,834 B2**
(45) **Date of Patent: Apr. 28, 2009**

(54) **STERILE POWDERS, FORMULATIONS, AND METHODS FOR PRODUCING THE SAME**

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(30) **Foreign Application Priority Data**

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(58) **Field of Classification Search** 424/489; 540/63, 120; 514/169, 174, 177–182
See application file for complete search history.

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(57) **ABSTRACT**

The invention provides sterile glucocorticosteroids and sterile formulations containing glucocorticosteroid and use thereof in the treatment of an allergic and/or inflammatory condition of the nose or the lungs.

85 Claims, No Drawings

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STERILE POWDERS, FORMULATIONS, AND METHODS FOR PRODUCING THE SAME

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. Ser. No. 09/230,781, filed Jan.29, 1999 (now U.S. Pat. No. 6,392,036), which is the National Stage application of International Application No. PCT/SE98/02039, filed Nov. 11, 1998, which claims the benefit of Swedish Patent Application No. 9704186-7, filed Nov. 14, 1997. The contents of these applications are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

This invention relates to a process for sterilization of a powderderd form of a glucocortico-steriod, sterile glucocorticosteroids, sterile formulations containing glucocorticosteroids and use thereof in the treatment of an allergic and/or inflammatory condition of the nose or lungs.

BACKGROUND OF THE INVENTION

Various methods have been proposed in the past for the sterilization of glucocorticosteroids. PT-A-69652 discloses the cold sterilization of micronized glucocorticosteroids using mixtures of ethylene oxide and carbon dioxide, since, according to PT-A-69652, steroids in powder form are not stable at temperatures above 60° C. Specific examples of glucorticosteroids are prednacindone, dexamethasone and prednisolone, and salts, esters and fluoro derivatives thereof, including dexamethasone acetate, dexamethasone phosphate, prednisolone pivalate and 9-alphafluoro prednisolone. However, ethylene oxide is toxic and when it is used to sterilize glucocorticosteroids it has been found that the residual amounts of the ethylene oxide contravene pharmaceutical guidelines which require very low levels of residual ethylene oxide. Accordingly this method has been found to be unsuitable for producing therapeutically acceptable glucocorticosteroids and formulations thereof.

U.S. Pat. No. 3,962,430 discloses a method for the production of sterile isotonic solutions of medicinal agents, which comprises adding the agent to a saturated solution of sodium chloride in water at 100° C. and then heating the mixture at 100-130° C. This method is not suitable for suspensions of fine particles of glucocorticosteroids which are intended for inhalation because the water, and the heating and cooling involved, produce unfavorable changes in the size of the particles. Indeed it can lead to the formation of bridges between the fine particles producing large, hard aggregates which will not deaggregate into the desired fine particles upon administration.

A putative alternative is dry heat sterilization. According to the European Pharmacopoeia (1996, pp. 283-4) a normal heat sterilization process runs at 180° C. for 30 min or at a minimum of 160° C. for at least 2 hours. According to Pharmacopoeia Nordica (1964, pp. 16) such a sterilization can be carried out at 140° C. for 3 hours. However at the temperatures of these processes glucocorticosteroids suffer significant degradation and are subject to changes in their surface structure.

Sterilization by β- or γ-irradiation is also known. Indeed Illum and Moeller in Arch. Pharm. Chemi. Sci., Ed. 2, 1974, pp. 167-174 recommend the use of such irradiation to sterilize glucocorticosteroids. However when such irradiation is used to sterilize certain finely divided, e.g. micronized, glucocorticosteroids, they are significantly degraded.

WO-A-96/09814 to Andaris Ltd. relates to spray-dried particles of a water-soluble material with a mass median particle size of 1 to 10 μm. The aim of the invention is to produce uniform and reproducible particles for use in dry powder inhalers. The water-soluble material is preferably a human protein or a fragment thereof, in natural or recombinant form, e.g. human serum albumin (HSA), alpha-1 antitrypsin or alcohol dehydrogenase. Also combinations of an active material with a carrier were produced e.g. budesonide and lactose. It is stated generally that the microparticles produced can be sterile without teaching how this could or would be achieved nor showing any proof thereof.

WO-A-96/32095 to Astra AB relates to a process for the preparation of respirable particles by dissolving an inhalation compound in a solvent, introducing the resulting solution containing the inhalation compound in droplet form or as a jet stream into an anti-solvent which is miscible with the solvent and which is under agitation. Budesonide with a mass median diameter (MMD) of less than 10 μm is produced with the process. There is no information in WO-A-96/32095 about sterilization or sterile particles.

WO-A-92/11280 to Instytut Farmaceutyczny relates to a method of obtaining (22R) diastereoisomer of budesonide by a condensation reaction followed by crystallizing the crude product of condensation from ethanol. The obtained 21-acetate of budesonide (22R) is hydrolyzed and the product thus obtained is crystallized from ethyl acetate. The content of (22S) diastereoisomer of budesonide is 1% or less. There is no information in WO-A-92/11280 about sterilization or sterile particles.

We have also found that attempts at terminal sterilization of the pharmaceutical formulations, especially suspensions, e.g. aqueous suspensions, of glucocorticosteroids have all proved unsatisfactory. Such suspensions can not normally be sterilized by sterile filtration as most of the particles of glucocorticosteroid will be retained on the filter. We have also shown that moist heat sterilization, e.g. steam treatment of glass vials containing the product, leads to an unacceptable change in particle size.

Various aqueous suspensions of finely divided glucocorticosteroids are known, e.g. the budesonide-containing product known as Pulmicort® nebulising suspension. (Pulmicort® is a trademark of Astra AB of Sweden). Similar formulations of fluticasone propionate are known from WO-A-95/31964.

Accordingly a new process for the sterilization of glucocorticosteroids (and formulations containing them) is required.

Surprisingly we have now found that effective sterilization of dry glucocorticosteroids can be carried out at a significantly lower temperature than that considered necessary for the heat sterilization of other substances. Such sterile glucocorticosteroids can be used in the preparation of sterile formulations containing them.

DESCRIPTION OF THE INVENTION

According to the invention there is provided a process for the sterilization of a glucocorticosteroid, which process comprises heat treating the glucocorticosteroid in the form of a powder at a temperature of from 100 to 130° C. The process is preferably carried out at a temperature of from 110 to 120° C., more preferably at about 110° C., preferably for up to about 24 hours, more preferable up to 10 hours, e.g. from 1 to 10 hours. The process is conveniently carried out under atmospheric conditions, i.e. in air, but may also be carried out under an inert gas atmosphere, e.g. an atmosphere of argon or nitrogen.

Surprisingly we have found that this process kills many more spores when applied to the glucocorticosteroid budesonide than when applied to the comparison substance calcium stearate. Even better results were obtained with the glucocorticosteroid rofleponide.

It is believed, but we do not intend to be limited by this explanation, that the unexpectedly low temperature at which the glucocorticosteroids can be sterilized indicates that the glucocorticosteroid may provide some synergistic effect, when taken together with the heat treatment, in destroying the spores.

The glucocorticosteroid used in the invention is preferably an anti-inflammatory glucocorticosteroid, e.g. for use in nasal and oral inhalation. Examples of glucocorticosteroids which may be used in the present invention include betamethasone, fluticasone (e.g. as propionate), budesonide, tipredane, dexamethasone, beclomethasone (e.g. as dipropionate), prednisolone, fluocinolone, triamcinolone (e.g. as acetonide), momethasone (e.g. as furoate), rofleponide (e.g. as palmitate), flumethasone, flunisolide, ciclesonide, deflazacort, cortivazol, 16α, 17α-butylidenedioxy-6α,9α-difluoro-11β,21-dihydroxy-pregna-1,4-diene-3,20-dione; 6α,9α-difluoro-11β-hydroxy-16α,17α-butylidenedioxy-17β-methylthioandrosta-4-ene-3-one; 16α,17α-butylidenedioxy-6α,9α-difluoro-11β-hydroxy-3-oxo-androsta-1,4-diene-17β-carbothioic acid S-methyl ester; methyl 9α-chloro-6α-fluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxy-6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxy-androsta-1,4-dien-17β-carbothioic acid S-(2-oxo-tetrahydrofuran-3-yl) ester; optionally in their pure isomeric forms (where such forms exist) and/or in the form of their esters, acetals or salts, where applicable. Suitably, use is made of momethasone furoate, beclomethasone dipropionate or fluticasone propionate or glucocorticosteroids with an asymmetric acetal structure, i.e. comprising 16α,17α-butylidenedioxy, such as budesonide, rofleponide or rofleponide palmitate. Preferably, use is made of budesonide, rofleponide or rofleponide palmitate and most preferably of budesonide.

The glucocorticosteroid is preferably used in the form of a finely divided, e.g. micronized, powder, particularly in the form of finely divided particles having a mass median diameter of less than 10 μm, more preferably less than 5 μm. The glucocorticosteroid may alternatively be in an ultra fine form, e.g. having a mass median diameter of less than 1.0 μm. The finely divided particles may be produced by conventional techniques known per se. e.g. by micronization or by direct precipitation. Information about micronization can be found e.g. in "The Theory and Practice of Industrial Pharmacy", Lachman, Liebermann and Klang, 2nd Ed., 1976, Lea & Febiger, Philadelphia, USA.

The temperature, time, batch size and type of sterilizer used will be interdependent. Thus generally the higher the temperature used in the process according to the invention, the less time is required to sterilize the glucocorticosteroid. The process is preferably carried out for no more than 8 hours, e.g. from 1 to 8 hours, when the temperature is greater than about 110° C., more preferably no more than 4 hours. At a temperature of about 120° C. the process is preferably carried out for no more than 4 hours, e.g. from 1 to 4 hours. more preferably no more than 2 hours, e.g. from 1 to 2 hours.

At temperatures of from about 110° C. up to 130° C., a batch of 50 g of glucocorticosteroid may suitably be heat treated from 1 to 4 hours. If desired sub-batches, e.g. of 4×50 g, may be used.

The present process may be carried out such that it results in a more than log 4 reduction in the amount of heat resistant spores. The process of the present invention is suitably carried out such that it results in a log 6 reduction in the amount of heat resistant spores. The present process is preferably carried out such that it results in a more than log 6 reduction, and more preferably such that it results in a more than log 7 reduction in the amount of heat resistant spores.

A different way of characterizing the efficiency of a sterilizing process is by using the D value. The D value, also known as the D_T value, is the time (in minutes) required to reduce ("kill") a standardized population of spores by 90% or 1 log cycle, i.e. to a survival fraction of 1/10, at a specific temperature T (in ° C.).

The present process may be carried out such that the D value is less than about 240 min at the preselected temperature T, wherein T is in the range of from 100 to 130° C. The process of the present invention is suitably carried out such that the D value is less than 150 min at the preselected temperature T. Preferably, the process of the present invention is carried out such that the D value is less than 90 min at the preselected temperature T, and more preferably such that the D value is less than 30 min at the preselected temperature T. T is suitably 100, 110, 120 or 130° C.

The sterilization process is desirably carried out in such a manner that all parts of the bulk of the glucocorticosteroid reaches, and is maintained within, the desired temperature for the desired time.

The present process may be carried out batch wise or continuously, preferably batch wise.

The glucocorticosteroid starting material for the process, which material may be in finely divided form, is suitably substantially dry, i.e. containing less than about 1% (w/w) of water. Preferably, the starting material for the process contains less than 0.5% (w/w) of water, and more preferably less than 0.3% (w/w) of water.

The glucocorticosteroid starting material for the process suitably has a bioburden of less than 50 CFU (colony forming units) per gram. The glucocorticosteroid starting material for the process preferably has a bioburden of less than 10 CFU per gram, more preferably of less than 1 CFU per gram.

According to the invention there is further provided a sterile glucocorticosteroid (e.g. budesonide), suitably dry and preferably in the form of finely divided particles, e.g. having a mass median diameter of less than 10 μm, and more preferably less than 5 μm.

By the term "sterile" we mean a product which meets the criteria of sterility according to the US Pharmacopoeia 23/NF18, 1995, pp. 1686-1690 and 1963-1975, and which provides a therapeutically acceptable glucocorticosteroid and formulations thereof. Further regulations for sterility of the final product include the European Pharmacopoeia (Ph. Eur. 1998, Chapters 2.6.1 and 5.1.1), the British Pharmacopoeia (BP 1993, Appendix XVI A, p. A180 and Appendix XVIII A, p. A 184) and the Japanese Pharmacopoeia (JP, 13th ed., pp. 69-71 and 181-182). Preferably, the therapeutically acceptable glucocorticosteroid and formulations thereof have been produced by a method which provides assurance of sterility according to the US Pharmacopoeia 23/NF18, 1995, pp. 1686-1690 and 1963-1975.

The glucocorticosteroid according to the invention will essentially maintain the same pharmacological activity and physico-chemical properties/its chemical purity and physical form as the starting material from which it is prepared, i.e. the degradation, and especially the chemical degradation, caused by the present sterilization process will be limited.

The glucocorticosteroid according to the invention is preferably at least 98.5% by weight pure, more preferably at least 99% by weight pure, and most preferably at least 99.2% by weight pure.

The invention further provides a sterile glucocorticosteroid, preferably an anti-inflammatory glucocorticosteroid, more preferably budesonide, rofleponide or rofleponide palmitate, and most preferably budesonide, for use in the treatment of an allergic and/or inflammatory condition of the nose or lungs, e.g. chronic obstructive pulmonary disease (COPD), rhinitis or asthma. The invention also provides the use of such a sterile glucocorticosteroid, preferably an anti-inflammatory glucocorticosteroid, more preferably budesonide, in the manufacture of a medicament (preferably a sterile medicament) for use in the treatment of such conditions.

According to the invention there is further provided a sterile pharmaceutical formulation comprising a glucocorticosteroid in an aqueous suspension, wherein the glucocorticosteroid is preferably a sterile finely divided glucocorticosteroid, such as budesonide.

According to the invention there is also provided a sterile pharmaceutical formulation comprising a glucocorticosteroid and one or more pharmaceutically acceptable additives, to diluents or carriers. Examples of such additives include surfactants, pH regulating agents, chelating agents, agents rendering the suspension isotonic and thickening agents.

To obtain an efficient dispersion of the glucocorticosteroid particles in the suspension, a surfactant may be used, optionally in combination with e.g., lecithin. The surfactants may also function as stabilizing agents in the formulations according to the present invention. Examples of suitable surfactants include non-ionic surfactants of the alkyl aryl polyether alcohol type, specifically tyloxapol —a polymer of 4-(1,1,3,3-tetramethylbutyl)phenol with ethylene oxide and formaldehyde. Further suitable surfactants include sorbitan derivatives, e.g. polyoxyethylene sorbitan fatty acid esters, preferably of the polysorbate or Tween™ groups, more preferably polysorbate 80 or polyoxyethylene 20 sorbitan monooleate (Tween™ 80). Suitable surfactants also include polyoxyethylene ethers, especially polyoxyethylene alkyl ethers, preferably pentaethyleneglycol mono n-dodecylether or $C_{12}E_5$. Further suitable surfactants include poloxamers, polyoxyethylene castor oil derivatives, polyvinylalcohol and block copolymers of polyethyleneoxides, polypropyleneoxides, polybutyleneoxides and polyethyleneglycols (PEGs) or mixtures of any of these. Further suitable surfactants include polyethylene glycol derivatives, especially polyethylene glycol 660 hydroxystearate or Solutol™ HS 15, povidone, polyvinylpyrrolidone (PVP) and polyethyleneglycols (PEGs).

The surfactant may be present at about 0.002 to 2% w/w of the formulation. We prefer the polyoxyethylene sorbitan fatty acid esters to be present at about 0.005 to 0.5% w/w, poloxamers at about 0.01 to 2% w/w, and polyoxyethylene alkyl ethers or thepolyoxy-ethylene castor oil derivatives at about 0.01 to 1.0% w/w of the formulation.

The pH of the suspension may be adjusted as required. Examples of suitable pH regulating agents are weak organic acids, e.g. citric acid, strong mineral acids, e.g. hydrochloric acid, and strong alkaline agents. e.g. NaOH. Alternatively, the pH of the system can be adjusted by balancing the acid and salt forms of buffers such as citric acid, sodium citrate, acetic acid, sodium acetate and sodium phosphate. We prefer the formulations intended for inhalation to have a pH in the range of from about 3.5 to about 6.0, more preferably from 4.0 to 5.0, and most preferably from 4.2 to 4.8.

We also prefer the formulation to contain a suitable chelating agent, e.g. disodium edetate (EDTA). The chelating agent may be present at about 0.005 to 0.1% w/w of the formulation.

Agents which make the suspension isotonic may be added. Examples are dextrose, glycerol, mannitol, sodium chloride, potassium chloride and sodium bromide.

In order to form a stable suspension with a minimal tendency to agglomerate or form a sediment, a thickening agent may be included in the formulation. Examples of suitable thickening agents are cellulose derivatives, suitably cellulose ethers, or microcrystalline cellulose. Preferred cellulose ethers include ethylcellulose, ethylmethylcellulose, hydroxyethylcellulose, hydroxyethylmethylcellulose, hydroxyethylethylcellulose, methylcellulose, hydroxymethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose and carboxymethylcellulose (CMC), e.g. the sodium salt thereof. Suitable thickening agents also include cyclodextrin and dextrin. Suitable thickening agents further include xanthan gum, guar gum and carbomer. Preferred thickening agents in the formulations of the invention are povidone, polyvinylpyrrolidone (PVP) and polyethyleneglycols (PEGs).

The thickening agent may be present at about 0.1 to 3.0% w/w of the formulation. Preferably microcrystalline cellulose and sodium carboxymethyl cellulose (CMC) are present at about 0.5 to 2.5%, xanthan gum at about 0.3 to 3%, carbomer at about 0.1 to 2%, guar gum at about 0.3 to 2% and hydroxypropyl methyl cellulose at about 0.5 to 3.0%, w/w of the formulation.

In the suspension the active constituent, e.g. budesonide, is present as small particles, where at least 90% of the small particles have a mass median diameter (MMD) of less than 20 μm, suitably at least 80% less than 10 μm, preferably at least 70% less than 7 μm and most preferably at least 60% less than 4 μm.

We prefer the suspension to contain from about 0.05 to about 20 mg/ml of the glucocorticosteroid. More preferably the suspension contains from 0.08 to 10 mg/ml of the glucocorticosteroid and most preferably from 0.1 to 5 mg/ml of the glucocorticosteroid.

A sterile pharmaceutical formulation comprising a glucocorticosteroid, such as finely divided budesonide, rofleponide or rofleponide palmitate, sterilized according to the present process, can be prepared by mixing the sterilized glucocorticosteroid with any suitable additional ingredient, e.g. a surfactant, a pH regulating or chelating agent, an agent rendering the suspension isotonic or a thickening agent. All components, other than the glucocorticosteroid, can be produced by sterile filtration of their aqueous solutions. The resulting sterile suspension may be stored under an over pressure of a sterile and inert gas, e.g. nitrogen or argon, and should be filled under aseptic conditions into pre-sterilized containers to produce a sterile pharmaceutical product, e.g. using a blow/fill/seal system.

The invention further provides a method for treatment of an inflammatory condition of the nose or lungs by administering to a mammal, especially a human being, suffering from such a condition a therapeutically effective amount of a sterile glucocorticosteroid or a sterile formulation containing a glucocorticosteroid, preferably a sterile formulation containing a sterile glucocorticosteroid produced according to the present invention. More specifically, the invention provides a method for treatment of chronic obstructive pulmonary disease (COPD), rhinitis, asthma or other allergic and/or inflammatory conditions by administering to a mammal, especially a human being, suffering from such a condition a therapeutically effective amount of a sterile glucocorticosteroid or a sterile formulation containing a glucocorticosteroid, preferably a sterile formulation containing a sterile glucocorticosteroid produced according to the present invention.

EXAMPLES

The invention is illustrated by reference to the following Examples which are not intended to limit the invention.

Example 1

Experiments were carried out to determine the effect of heat treatment upon the chemical purity and physical form of samples of micronized budesonide.

Nine 50 g batches of micronized budesonide (sample nos. 2-10 in Table 1 below) were subjected to the heat treatment shown in Table 1 in a dry sterilizer, Lytzen model CB 1200. Sample 1 was not subjected to such treatment and was used as the reference sample. After the treatment the samples were analyzed for chemical and physical properties.

TABLE 1

No.	1	2	3	4	5	6	7	8	9	10
Temp/° C.	—	100	100	100	110	110	110	120	120	120
Time/hours	0	4	6	10	2	4	10	1	2	4
Size/μm	2.0	2.2	2.2	2.2	2.2	2.2	2.3	2.2	2.2	2.3
Size range (10-90%)/μm	2.6	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Epimer A/% by wt	48.8	48.8	48.7	48.7	48.7	48.8	48.7	48.7	48.7	48.7
Budesonide content/% by wt	99.4	99.3	99.3	99.2	99.2	99.3	98.9	99.2	99.2	99.0
Total of known foreign steroids	0.13	0.14	0.16	0.15	0.16	0.15	0.18	0.14	0.15	0.17
Total of unknown foreign steroids	0.04	0.04	0.05	0.05	0.04	0.08	0.18	0.04	0.07	0.16

After the heat treatment there was no change in the Brunauer, Emett and Teller (BET) surface value (as measured using a Micrometrics Gemini 2375 device; see also British Standard 4359 (1969) part 1) of the budesonide or in its X-ray diffraction pattern for each sample compared to sample 1. The size for each sample was measured as the mass median diameter (MMD) using a Coulter counter.

Example 2

The sterilization of budesonide was compared with that of calcium stearate.

Samples of 0.5 g of budesonide and of 0.5 g of calcium stearate were each inoculated with 0.1 ml of a Steris *Bacillus subtilis* (*globigii*) (Lot#LG126B) spore suspension containing 1.5×10^7 spores. Each sample was subjected to a temperature of 110° C. for 3 hours and 10 min in a Baxter Constant Temperature Oven using the same technique as in Example 1. The spore population of the samples was measured and the results obtained are shown below in Table 2.

TABLE 2

Compound	Before	After
Calcium stearate	1.5×10^7 spores	3.3×10^6 spores
Budesonide	1.5×10^7 spores	<10 spores

As a result of the heat treatment, a spore log reduction of greater than 6.2 was obtained in the inoculated sample of budesonide, whereas the log reduction was less than 0.7 in the inoculated sample of calcium stearate.

Example 3

Tests were performed to evaluate the heat resistance of various naturally occurring microorganisms.

Samples of 0.5 g of budesonide powder were each inoculated with approximately 10^2-10^3 viable ATCC microorganisms in 120 ml open-ended polypropylene container. Each sample was subjected to a temperature of 110° C. for 3 hours and 10 min. The microorganism population of the samples was measured before and after heat treatment and the results obtained are shown below in Table 3.

TABLE 3

Microorganism	Before	After
E. coli	450	0
B. subtilis ATCC 6633	300	0
Salmonella typhi	270	0
C. albicans	780	0
A. niger	260	0
M. luteus	300	0
S. epidermidis	240	0
C. sporegenes	160	0
Ps. Aeruginosa	350	0
B. subtilis ATCC 6633	1.2×10^5	1[1]

[1]A singular *bacillus* species was found, verified by Gram stain in the 10^0 dilution plate.

As is evident from Table 3, heat treatment of budesonide at 110° for 3 hours and 10 min, is an effective sterilizing method for a substantial variety of microorganisms.

Example 4

A formulation comprising finely divided budesonide sterilized by the method of Example 2, and meeting the criteria of sterility according to the US Pharmacopoeia 23/NF18, 1995, was prepared by mixing the following ingredients:

TABLE 4

Micronized budesonide	0.125 mg
Disodium edetate	0.1 mg
Sodium chloride	8.5 mg
Polysorbate 80	0.2 mg
Anhydrous citric acid	0.28 mg

TABLE 4-continued

Sodium citrate	0.5 mg
Purified water	to 1 ml

All the components, other than the budesonide, were produced by sterile filtration of their aqueous solutions and an appropriate volume of the resulting suspension (about 2 ml) was filled under aseptic conditions into pre-sterilized 5 ml containers to produce a sterile product.

The resulting suspension may be stored under an overpressure of sterile nitrogen and may be filled into containers using a blow/fill/seal system.

Example 5

A sterile formulation comprising finely divided budesonide sterilized by the method of Example 2, can be prepared by mixing the following ingredients:

TABLE 5

Micronized budesonide	2-3 mg
Disodium edetate	0.1 mg
Sodium chloride	8.5 mg
Stabilizing agent	0.02-2 mg
Anhydrous citric acid	0.28 mg
Sodium citrate	0.5 mg
Purified water	to 1 ml

All the components, other than the budesonide, can be produced by sterile filtration of their aqueous solutions and an appropriate volume of the resulting suspension (about 2 ml) filled under aseptic conditions into pre-sterilized 5 ml containers to produce a sterile product.

The resulting suspension may be stored under an overpressure of sterile nitrogen and may be filled into containers using a blow/fill/seal system.

Example 6

5 g of micronized budesonide was inoculated with approximately 2 ml of a spore suspension of *Bacillus subtilis*.

The substance and the spore suspension were mixed and dried for approximately 3 hours at 55° C. The inoculated and dried budesonide was mixed with 20-40 g of non-inoculated micronized budesonide.

5 g portions of this sample were heat treated at 100° C., 110° C. or 120° C. in a Heraeus ST 5060 heating apparatus. A 1 g sample was withdrawn after various heating times at the respective heating temperatures. Each such 1 g sample was transferred to 10 ml of dilution medium pH 7.2. Appropriate dilutions were made in 0.1% Peptone Aqueous solution and the number of spores/g were determined by a pour plate technique according to US Pharmacopoeia 23/NF18, 1995, pp. 1681-1686, especially p. 1684.

The number of spores before heat treatment were determined in samples heated at 80° C. for 10 min in order to kill the vegetative cells.

The results are shown in Table 6. where the D_T value is the amount of time in minutes required to obtain a log 1 reduction in the number of spores before and after heat treatment at the temperature T (in ° C.).

TABLE 6

	Heating at 100° C.			
	80° C.	Heating time at 100° C.		
	10 min	15 min	45 min	75 min
spores/g	6.5×10^6	4.8×10^3	7.1×10^2	1.7×10^2
log spores/g	6.81	3.68	2.85	2.23
	Heating at 110° C..			
	80° C.	Heating time at 110° C.		
	10 min	5 min	15 min	20 min
spores/g	2×10^6	2.08×10^4	9.25×10^2	3.55×10^2
log spores/g	6.20	4.32	2.97	2.55
	Heating at 120° C.			
	80° C.	Heating time at 120° C.		
	10 min	4 min	6 min	8 min
spores/g	1.5×10^6	1.9×10^2	5.5×10^1	2×10^1
log spores/g	6.19	2.28	1.74	1.30

D_{100} = 41.5 min; correlation coefficient = −0.0996 This means that it takes 6 × 41.5 minutes to obtain a log 6 reduction in the number of spores at a temperature of 100° C.
D_{110} = 8.3 min; correlation coefficient = −0.995 This means that it takes 6 × 8.3 minutes to obtain a log 6 reduction in the number of spores at a temperature of 110° C.
D_{120} = 4.1 min; correlation coefficient = −0.998 This means that it takes 6 × 4.1 minutes to obtain a log reduction in the number of spores at a temperature of 120° C.

Example 7

1 g of micronized budesonide, prednisolone and beclomethasone dipropionate and 0.5 g of rofleponide were inoculated with a different spore suspension to the one used in Example 6.

The samples were heat treated at 110° C. A sample was withdrawn after various heating times. The number of spores/g were determined by a pour plate technique according to US Pharmacopoeia 23/NF18, 1995, pp. 1681-1686, especially p. 1684.

From the number of spores before and after heat treatment the log reduction of spores and decimal reduction time (time needed at a specified temperature to reduce the number of microorganisms with one log) was calculated.

The results are shown in Table 7.

TABLE 7

	Heating at 110° C.
Glucocorticosteroid	D_{110} value in min
Budesonide	41
Rofleponide	9.8
Beclomethasone dipropionate	72.7
Prednisolone	73.8

Table 7 clearly shows that the present process is very efficient in reducing the number of spores in samples containing glucocorticosteroids. The process is especially efficient with budesonide and rofleponide. In fact analysis conducted on a full 1.0 g sample of rofleponide yielded total kill at very short cycle times (≧5 minutes at 110° C.), where a D_{110} value could not be calculated.

Comparative Example 8

Irradiation

About 3 g of micronized budesonide substance stored in a plastic container, were subjected to irradiation. The substance was exposed to β-irradiation at 2.5 to 25 kGy and γ-irradiation at 8 to 32 kGy. After the exposure the budesonide content and the amount of related substances were determined by liquid chromatography. The chemical stability of budesonide was considered to be the most critical parameter to study.

TABLE 8

Stability of micronized budesonide substance during sterilization by irradiation

Exposure Intensity (kGy)	Ref. i)	β 2.5	β 5	β 10	β 17	β 25	γ 7.8	γ 31.9
Budesonide content (%)	99.5-99.8	99.1	98.9	98.9	98.8	98.8	97.9	95.0
Related substances								
Total of known foreign steroids	0.13-0.15	0.19	0.19	0.18	0.20	0.21	0.34	0.51
Total of unknown foreign steroids	0.03-0.04	0.19	0.24	0.26	0.36	0.43	0.68	1.8

i) The analysis was done on different days and the reference was analyzed at all occasions

From the results in Table 8, it can be seen that the budesonide content decreases in samples exposed to β- and γ-irradiation. Several new degradation products were observed, especially for the γ-irradiated sample. In addition the mass balance for both β- and γ-irradiated samples is poor. The budesonide content has decreased by 0.5-4.6 percent, when exposed to β- or γ-irradiation.

It can be concluded that micronized budesonide can not be satisfactorily sterilized with β- or γ-irradiation, due to significant chemical degradation.

The invention claimed is:

1. A pharmaceutically acceptable, micronized powder composition at least 98.5% by weight of which is pure budesonide or an ester, acetal or salt thereof, wherein the composition meets the criteria of sterility according to the US Pharmacopoeia 23/NF18, 1995, pages 1686-1690 and 1963-1975.

2. The composition of claim 1, wherein at least 98.5% of the composition is pure budesonide.

3. The composition of claim 1, wherein at least 99% by weight of the composition is pure budesonide or an ester, acetal or salt thereof.

4. The composition of claim 1, wherein at least 99.2% by weight of the composition is pure budesonide or an ester, acetal or salt thereof.

5. The composition of claim 1, wherein the composition is in the form of particles having a mass median diameter (MMD) of less than 10 μm.

6. The composition of claim 5, wherein the particles have a MMD of less than 5 μm.

7. The composition of claim 5, wherein the particles have a MMD of less than 1 μm.

8. The composition of claim 5, wherein at least 99% by weight of the composition is pure budesonide or an ester, acetal or salt thereof.

9. The composition of claim 5, wherein at least 99.2% by weight of the composition is pure budesonide or an ester, acetal or salt thereof.

10. The composition of claim 1, wherein the composition is in the form of particles at least 80% of which have a MMD of less than 10 μm.

11. The composition of claim 10, wherein at least 99% by weight of the composition is pure budesonide or an ester, acetal or salt thereof.

12. The composition of claim 10, wherein at least 99.2% by weight of the composition is pure budesonide or an ester, acetal or salt thereof.

13. The composition of claim 10 wherein at least 70% of the particles have a MMD of less than 7 μm.

14. The composition of claim 13, wherein at least 99% by weight of the composition is pure budesonide or an ester, acetal or salt thereof.

15. The composition of claim 13, wherein at least 99.2% by weight of the composition is pure budesonide or an ester, acetal or salt thereof.

16. The composition of claim 10 wherein at least 60% of the particles have a MMD of less than 4 μm.

17. The composition of claim 16, wherein at least 99% by weight of the composition is pure budesonide or an ester, acetal or salt thereof.

18. The composition of claim 16, wherein at least 99.2% by weight of the composition is pure budesonide or an ester, acetal or salt thereof.

19. The composition of claim 1, wherein the budesonide is isomerically pure.

20. The composition of claim 19, wherein the budesonide is in the form of the (22R) diastereoisomer.

21. A method for the treatment of an inflammatory condition, the method comprising administering to a mammal suffering from such a condition a therapeutically effective amount of the composition of claim 1.

22. A method for the treatment of an inflammatory condition, the method comprising administering to a mammal suffering from such a condition a therapeutically effective amount of the composition of claim 2.

23. The method of claim 21, wherein the mammal is a human being.

24. A method for the treatment of chronic obstructive pulmonary disease (COPD), the method comprising administering to a mammal suffering from COPD a therapeutically effective amount of the composition of claim 1.

25. A method for the treatment of COPD, the method comprising administering to a mammal suffering from COPD a therapeutically effective amount of the composition of claim 2.

26. The method of claim 24, wherein the mammal is a human being.

27. A method for the treatment of rhinitis, the method comprising administering to a mammal suffering from rhinitis a therapeutically effective amount of the composition of claim 1.

28. A method for the treatment of rhinitis, the method comprising administering to a mammal suffering from rhinitis a therapeutically effective amount of the composition of claim 2.

29. The method of claim 27, wherein the mammal is a human being.

30. A method for the treatment of asthma, the method comprising administering to a mammal suffering from asthma a therapeutically effective amount of the composition of claim 1.

31. A method for the treatment of asthma, the method comprising administering to a mammal suffering from asthma a therapeutically effective amount of the composition of claim 2.

32. The method of claim 30, wherein the mammal is a human being.

33. A method for the treatment of an allergic condition, the method comprising administering to a mammal suffering from an allergic condition a therapeutically effective amount of the composition of claim 1.

34. A method for the treatment of an allergic condition, the method comprising administering to a mammal suffering from an allergic condition a therapeutically effective amount of the composition of claim 2.

35. The method of claim 33, wherein the mammal is a human being.

36. The method of claim 21, wherein the budesonide is isomerically pure.

37. The method of claim 36, wherein the budesonide is in the form of the (22R) diastereoisomer.

38. A pharmaceutically acceptable, sterilized powder composition at least 98.5% by weight of which is pure budesonide or an ester, acetal or salt thereof, wherein the sterilized powder composition was produced by sterilization of viable-microorganism-containing particles of budesonide or an ester, acetal or salt thereof.

39. The composition of claim 38, wherein at least 98.5% by weight of the composition is pure budesonide.

40. The composition of claim 38, at least 99% by weight of which is pure budesonide or an ester, acetal or salt thereof.

41. The composition of claim 38, at least 99.2% by weight of which is pure budesonide or an ester, acetal or salt thereof.

42. The composition of claim 41, wherein the sterilization was accomplished by a method comprising heat sterilization.

43. The composition of claim 42, wherein the heat sterilization was carried out in air.

44. The composition of claim 42, wherein the heat sterilization was carried out under an inert gas atmosphere.

45. The composition of claim 42, wherein the heat sterilization was accomplished at a temperature of 100 to 130° C.

46. The composition of claim 42, wherein the heat sterilization was accomplished at a temperature of 110 to 120° C.

47. The composition of claim 42, wherein the heat sterilization was accomplished at a temperature of 110° C.

48. The composition of claim 38, wherein the budesonide is isomerically pure.

49. The composition of claim 48, wherein the budesonide is in the form of the (22R) diastereoisomer.

50. A pharmaceutically acceptable suspension consisting of a micronized powder composition at least 98.5% by weight of which is pure budesonide or an ester, acetal or salt thereof, suspended in an aqueous solution, wherein the suspension meets the criteria of sterility according to the US Pharmacopoeia 23/NF18, 1995, pages 1686-1690 and 1963-1975.

51. The pharmaceutically acceptable suspension of claim 50, wherein at least 98.5% by weight of the micronized powder composition is pure budesonide.

52. The pharmaceutically acceptable suspension of claim 50, wherein at least 99% by weight of the micronized powder composition is pure budesonide or an ester, acetal or salt thereof.

53. The pharmaceutically acceptable suspension of claim 50, wherein at least 99.2% by weight of the micronized powder composition is pure budesonide or an ester, acetal or salt thereof.

54. The suspension of claim 50, wherein one or more pharmaceutically acceptable ingredients selected from the group consisting of surfactants, pH regulating agents, chelating agents, agents that make the suspension isotonic, and thickening agents are dissolved in the aqueous solution.

55. The suspension of claim 54 comprising a surfactant that is a non-ionic surfactant, a sorbitan derivative, a polyoxyethylene ether, a polyoxyethylene castor oil derivative, or polyoxyethylene glycol, dissolved in the aqueous solution.

56. The suspension of claim 55, wherein the surfactant is present at about 0.002 to 2% w/w of the suspension.

57. The suspension of claim 55, wherein the surfactant is tyloxapol; polysorbate 80; or polyethylene glycol 660 hydroxystearate.

58. The suspension of claim 54 comprising a pH regulating agent that is a weak organic acid, mineral acid, strong alkaline agent or buffer.

59. The suspension of claim 58, wherein the pH regulating agent is citric acid, hydrochloric acid, NaOH, or sodium citrate.

60. The suspension of claim 58, wherein the suspension has a pH of about 3.5 to 6.0.

61. The suspension of claim 58, wherein the suspension has a pH of about 4.0 to 6.0.

62. The suspension of claim 58, wherein the suspension has a pH of about 4.2 to 4.8.

63. The suspension of claim 54, wherein a chelating agent is present at about 0.005 to 0.1% w/w of the suspension.

64. The suspension of claim 63, wherein the chelating agent is disodium edetate (EDTA).

65. The suspension of claim 54 comprising dextrose, glycerol, mannitol, or sodium chloride in an amount to make the solution isotonic.

66. The suspension of claim 54, wherein the aqueous solution comprises a thickening agent constituting about 0.1 to 3.0% w/w of the suspension.

67. The suspension of claim 66, wherein the thickening agent is ethyl cellulose, ethylmethylcellulose, cyclodextrin, dextrin, xanthan gum, providone, polyvinyiprovidone (PVP) or polyethyleneglycol (PEG).

68. A method for the treatment of an inflammatory condition, the method comprising administering to a mammal suffering from such a condition a therapeutically effective amount of the suspension of claim 50.

69. A method for the treatment of an inflammatory condition, the method comprising administering to a mammal suffering from such a condition a therapeutically effective amount of the suspension of claim 51.

70. The method of claim 68, wherein the mammal is a human being.

71. A method for the treatment of COPD, the method comprising administering to a mammal suffering from COPD a therapeutically effective amount of the suspension of claim 50.

72. A method for the treatment of COPD, the method comprising administering to a mammal suffering from COPD a therapeutically effective amount of the suspension of claim 51.

73. The method of claim 71, wherein the mammal is a human being.

74. A method for the treatment of rhinitis, the method comprising administering to a mammal suffering from rhinitis a therapeutically effective amount of the suspension of claim 50.

75. A method for the treatment of rhinitis, the method comprising administering to a mammal suffering from rhinitis a therapeutically effective amount of the suspension of claim 51.

76. The method of claim 74, wherein the mammal is a human being.

77. A method for the treatment of asthma, the method comprising administering to a mammal suffering from asthma a therapeutically effective amount of the suspension of claim 50.

78. A method for the treatment of asthma, the method comprising administering to a mammal suffering from asthma a therapeutically effective amount of the suspension of claim 51.

79. The method of claim 77, wherein the mammal is a human being.

80. A method for the treatment of an allergic condition, the method comprising administering to a mammal suffering from an allergic condition a therapeutically effective amount of the suspension of claim 50.

81. A method for the treatment of an allergic condition, the method comprising administering to a mammal suffering from an allergic condition a therapeutically effective amount of the suspension of claim 51.

82. The method of claim 80, wherein the mammal is a human being.

83. A pharmaceutically acceptable suspension consisting of a sterilized powder composition at least 98.5% by weight of which is pure budesonide or an ester acetal or salt thereof, suspended in an aqueous solution, wherein the sterilized powder composition was produced by sterilization of viable-microorganism-containing particles of budesonide or an ester, acetal or salt thereof, wherein the suspension meets the criteria of sterility according to the US Pharmacopoeia 23/NF18, 1995, pages 1686-1690 and 1963-1975.

84. The pharmaceutically acceptable suspension of claim 83, wherein at least 98.5% by weight of the powder composition is pure budesonide.

85. The pharmaceutically acceptable suspension of claim 83 wherein at least 99% by weight of the powder composition is pure budesonide or an ester, acetal or salt thereof.

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