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BY FEDERAL EXPRESS

Division of Dockets Management Branch (HFA-305)
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20857

CITIZEN PETITION

The undersigned Petitioner, Dey, L.P. ("Dey"), holder of New Drug Application ("NDA") 020950 for the inhalation solution drug DuoNeb®, submits this Citizen Petition, in quadruplicate, pursuant to Section 505(j)(5)(B)(iii) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §355(j)(5)(B)(iii), and FDA regulations §§ 21 C.F.R. §§ 314.95(a)(3), 10.20, 10.25 and 10.30.

A. Action Requested

This Citizen Petition requests a written determination by the Commissioner of Food and Drugs, head of the Food and Drug Administration ("FDA"), that Abbreviated New Drug Application ("ANDA") 76-724 filed by Ivax Pharmaceuticals, Inc. ("Ivax") for a generic formulation of DuoNeb® is subject to a 30-month stay of final approval, pursuant to the Federal Food, Drug, and Cosmetic Act ("FD&C Act"), 21 U.S.C. § 355(j)(5)(B)(iii) and FDA regulation 21 C.F.R. § 314.95(a)(3).

Dey believes such a 30-month stay is appropriate for the reasons set forth below, and requests FDA's written confirmation, in its ruling on this Petition, that this stay will be observed by the agency.

B. Statement of Grounds

1. Dey's NDA for DuoNeb®

On March 21, 2001, Dey received final approval to market the drug product DuoNeb®, an inhalation solution composed of the active ingredients albuterol and ipratropium, indicated for the treatment of bronchospasm associated with COPD in patients requiring more than one bronchodilator. Dey has been marketing DuoNeb® throughout the United States continuously since its approval.

2004P-0324

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2. U.S. Patent No. 6,632,842 B2

On December 28, 2001, two of Dey's employees filed a patent application in the U.S. Patent Office for an invention comprising DuoNeb® (albuterol and ipratropium inhalation solution system and kit) and a method for use of DuoNeb® for relieving COPD. This application ultimately issued into U.S. Patent No. 6,632,842 B2 ("the '842 patent") on October 14, 2003 (copy enclosed). The '842 patent has been assigned to Dey.

Within 30 days of issuance of the '842 patent, Dey submitted requisite information for the patent to FDA for listing in FDA's publication entitled "Approved Drug Products with Therapeutic Equivalence Evaluations" (known as "the Orange Book"), as required by the FD&C Act, 21 U.S.C. § 355(b)(1) and FDA regulation 21 C.F.R. §§ 314.53(b), (c). OGD then duly listed the '842 patent in the Orange Book. 21 U.S.C. § 355(b)(1), 21 C.F.R. § 314.53(e).

3. Ivax's ANDA for a Generic Version of DuoNeb®

On information and belief, in or about April, 2003 Ivax filed ANDA 76-724 for a generic version of DuoNeb®. Upon information and belief, Ivax's ANDA included a Paragraph I certification because at the time the application was filed, an application for the '842 patent was pending but the patent had not yet issued.

After the '842 patent issued on October 14, 2003, Ivax amended its patent certification to address the '842 patent. Ivax made a Paragraph IV certification against the '842 patent, alleging that the patent is invalid or will not be infringed by Ivax's generic formulation of DuoNeb®. On or about December 12, 2003, Dey received a notice letter from Ivax asserting the grounds for Ivax's Paragraph IV certification.

4. Dey's Paragraph IV Infringement Action

On January 26, 2004, within 45 days after receiving notice of Ivax's Paragraph IV certification, Dey timely commenced an action for infringement of the '842 patent by filing a complaint against Ivax pursuant to 35 U.S.C. § 271(e). On February 12, 2004, Ivax served an answer to Dey's complaint, and counterclaimed for a declaratory judgment that the '842 patent is invalid and will not be infringed.

This Paragraph IV litigation will now proceed at the same time as FDA conducts a substantive review of Ivax's ANDA.

5. A 30-Month Stay of Final Approval of Ivax's ANDA Should be Imposed

Under FDA regulation 21 C.F.R. § 314.95(a)(3), as amended effective August 18, 2003 (and 21 U.S.C. § 355(j)(5)(B)(iii) of the FD&C Act as then in force), the final approval of an ANDA is required to be stayed for 30 months from the date the holder of the NDA for the pertinent reference listed drug received the ANDA applicant's notice of a Paragraph IV certification against a listed Orange Book patent for the drug involved, provided the patent owner brings an infringement action against the ANDA applicant within 45 days after receiving the notice. This amended regulation provides for a limit of one 30-month stay per ANDA, even if subsequent patents are issued, listed, and made the basis of Paragraph IV infringement litigation. See 68 Fed.Reg. 36676, 36688 (June 18, 2003). The purpose of the amended rule was not only to avoid the abuse of multiple 30-month stays that would further delay generic competition, but also **"to ensure that our revised interpretation allows for one full opportunity for a 30-month stay after notice of a paragraph IV certification."** *Id.* (emphasis supplied).

In the instant situation: (i) the '842 patent is the only listed patent for DuoNeb®, (ii) Ivax's ANDA is the first ANDA to include a Paragraph IV certification against this patent, and (iii) Dey timely brought a Paragraph IV infringement action against Ivax. These facts should result in a 30-month stay of final FDA approval of Dey's ANDA for a generic version of DuoNeb®. That stay does not expire until June 12, 2006.¹

6. The Statutory Codification of the Single 30-Month Stay

Shortly after FDA finalized its single-month stay regulation, Congress amended 21 U.S.C. § 355(j)(5)(B)(iii) of the FD&C Act on December 8, 2003 to codify the principle of a single 30-month stay of final approval per ANDA. It was Congress' intent to clarify this limitation by statute, since some comments on FDA's proposal to amend its regulation to this

¹ Subsequently, Dey received Paragraph IV notice letters from Eon Labs, Inc., Breathe Ltd., Alharma USPD Inc. and Novex Pharma Division of Apotex, Inc., each informing Dey that the relevant company has also filed an ANDA for a generic version of DuoNeb® containing a Paragraph IV certification against the '842 patent. Dey has brought timely Paragraph IV infringement actions against Eon, Breathe Ltd. and Alharma, and intends to bring a timely such action against Novex Pharma. These ANDAs should each be subject to a 30-month stay as well, either because they were filed after issuance of the '842 patent (see 21 U.S.C. § 355(j)(5)(B)(iii) as recently amended) or, if filed before such issuance, for the reasons set forth in this petition.

effect had questioned whether the one 30-month stay restriction was statutorily authorized (particularly in light of FDA's prior interpretation that had permitted multiple 30-month stays). See 68 Fed. Reg. at 36692-36694.

It has come to Dey's attention that certain language in the statutory amendment effecting the single 30-month stay restriction might raise a question as to whether a 30-month stay is authorized for the precise situation presented with Ivax's ANDA, namely, a timely infringement action is brought by the owner of a single listed patent, which was applied for before, but issued shortly after, the relevant ANDA was submitted. In light of FDA's single 30-month stay regulation, its codification, and the legislative purpose of this codification, Dey maintains that a 30-month stay of final approval of Ivax's ANDA is fully warranted, for the following reasons.

a. The Statutory Amendment

The recently-enacted Medicare Prescription Drug Improvement and Modernization Act of 2003 ("the Medicare law"), includes various Hatch-Waxman reform provisions, including 21 U.S.C. § 355(j)(5)(B)(iii) as amended by Section 1101(a)(2)(A)(ii) of the Medicare law, which states in pertinent part:

If the applicant made [a paragraph IV certification]...the approval shall be made effective immediately unless, before the expiration of 45 days after the date on which the notice described in paragraph (2)(B) is received, **an action is brought for infringement of the patent that is the subject of the certification and for which information was submitted to the Secretary under subsection (b)(1) or (c)(2) before the date on which the application (excluding an amendment or supplement to the application), which the Secretary later determines to be substantially complete, was submitted...the approval shall be made effective upon the expiration of the thirty-month period beginning on the date of the receipt of the notice provided under paragraph (2)(B)(i) or such shorter or longer period as the court may order because either party to the action failed to reasonably cooperate in expediting the action...**(emphasis supplied)

Interpretation of this and all statutes is governed by a two-step test. First, it must be determined "whether Congress has spoken directly to the question at issue"; if so, "the agency must give effect to the unambiguously expressed intent of Congress." *Chevron, USA, Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 842-43 (1984). However, "if the statute is

silent or ambiguous with respect to a specific issue, the question...is whether the agency's answer is based on a permissible construction of the statute," under "the language of the statute, the legislative history, the agency regulations adopted to implement the statute and the agency comments regarding the regulations." *Id.* at 843; *Schering Corporation v. Food and Drug Administration*, 51 F.3d 390, 399 (3d Cir. 1995).

It is conceivable that the new "one 30-month stay per ANDA" statutory provision might be read to permit a 30-month stay of ANDA approval only if the patent is issued and listed before the ANDA is filed, when solely considering the wording: "patent that is the subject of the certification and for which information was submitted to the Secretary under subsection (b)(1) or (c)(2) before the date on which the application (excluding an amendment or supplement to the application), which the Secretary later determines to be substantially complete, was submitted." Nevertheless, amended 21 U.S.C. § 355(j)(5)(B)(iii) does not expressly prohibit a 30-month stay when an NDA holder's first patent claiming its reference listed drug is listed in the Orange Book and is the subject of a Paragraph IV challenge, but the listing and challenge happen to occur after the relevant ANDA is submitted. Thus, under *Chevron*, the legislative history of amended 21 U.S.C. § 355(j)(5)(B)(iii), and FDA's amended 30-month stay regulation, must be consulted for a proper interpretation.²

b. Pertinent Legislative History

A review of pertinent legislative history indicates that Congress' clear intent in enacting amended 21 U.S.C. § 355(j)(5)(B)(iii) was to codify FDA's above-cited regulation embodying the single 30-month stay principle, to eliminate the extensive delay in ANDA approvals caused by multiple 30-month stays arising from late-listed patents. There is also an indication that Congress based the single 30-month stay statutory provision in part on a Federal Trade Commission ("FTC") report which presumed the existence of an initial 30-month stay based on at least one patent having been listed prior to an ANDA submission. There is no clear

² Even if the new single-30-month stay statute explicitly spoke to the question, it must be disregarded if it would produce a result that is clearly contrary to Congress' intent, *United States v. Ron Pair Enterprises, Inc.*, 489 U.S. 235, 242 (1989), or it would produce an absurd result, which includes a result that is inconsistent with the clear intention of the statute's drafters. *Mova Pharm. Corp. v. Shalala*, 140 F.3d 1060, 1068 (D.C. Cir. 1998) ("if the literal application of a statute will produce a result demonstrably at odds with the intentions of the drafters, the intention of the drafters, rather than the strict language, controls"). See also *Environmental Defense Fund, Inc. v. Environmental Protection Agency*, 82 F.3d 451, 468-69 (D.C. Cir. 1996).

demonstration that Congress meant to prevent an NDA holder from entitlement to at least one 30-month stay for commencement of timely Paragraph IV infringement litigation. Indeed, no such prohibition was explicitly addressed in the legislative history.

Senator Orrin Hatch (R-Utah), in remarks on the Hatch-Waxman reform provisions of the Medicare law, emphasized that the statutory single 30-month stay provision codified FDA's amended 30-month stay regulation, which, as noted above, allows one 30 month stay per ANDA, without qualification:

“Medicare legislation that passed the House and Senate earlier this year **included the codification of the new FDA rule modifying the 30-month stay provision of Hatch-Waxman.**

Enactment of these provisions as part of the bipartisan agreement will lower prescription drug costs for millions of Americans by improving access to generic drugs, which are safe and effective and can be much less costly alternatives to brand-name prescription drugs.

A key component of the bipartisan agreement codifies the recent regulation that limits drug manufacturers to one and only one 30-month automatic stay in patent infringement litigation involving a generic drug application...”

149 Cong. Rec. S15533-02 *S15566, Nov. 22, 2003.

Similarly, Senator Edward Kennedy (D-Mass.) stressed that the 30-month stay provision of the Medicare law is intended to allow one 30-month stay per ANDA, again without qualification:

“Most significantly, the Hatch-Waxman provisions in this bill limit brand-name drug companies to only one 30-month stay of approval of generic drugs. This change will stop the multiple, successive 30-month stays that the Federal Trade Commission identified as having delayed approval of generic versions of several blockbuster drugs and cost consumers billions of dollars.”

149 Cong. Rec. S15882-03*S15884, Nov. 25, 2003.

And Senator Kennedy had noted the identical purpose for the predecessor Hatch-Waxman reform bill in the previous Congress:

“Schumer-McCain closes the evergreen loophole by permitting only one 30-month stay to apply to each generic drug.”

148 Cong. Rec. S8686-03 *S6828, July 16, 2002.

c. The FTC Report

Certain statements in the legislative history regarding the language of amended 21 U.S.C. § 355(j)(5)(B)(iii) suggest that the amended Hatch-Waxman provisions of the Medicare law are influenced in part by a report of the FTC entitled “Generic Drug Entry Prior to Patent Expiration: An FTC Study,” issued July 2, 2002. This FTC report recommended that there be only one automatic 30-month stay per drug product per ANDA to resolve infringement disputes over patents listed in the Orange Book prior to the filing date of the generic applicant’s ANDA. (July 2, 2002 Study, at ii-v).

Several comments on the legislation mention that the time of patent listing in the above-cited language of the amended 30-month stay statutory provision relates to the FTC report (Senator Hatch: “The one and only 30-month stay for all patents filed when the ANDA was submitted was also a centerpiece of the Federal Trade Commission report issued last summer”, Hearing, Senate Judiciary Committee on the Gregg-Schumer amendment to the Medicare bill, Aug. 1, 2003; FDA Chief Counsel Daniel Troy: “Both the Senate and the House bills amend Hatch-Waxman to allow only one 30-month stay per drug product, per ANDA for patents listed in the Orange Book prior to the generic company filing its ANDA. The FTC Study recommended this exact change.” *Id.*)

Significantly, however, the FTC report cited in the above comments recommended a single 30-month stay for already listed patents solely because the Commission’s factual model for this recommendation was premised on the existence of a previously listed patent, and the Commission was concerned about additional 30-month stays for new patents listed after ANDA submission. As the FTC report explains (FTC Study, July 2, 2002, at 40-41, emphasis supplied):

Timing of Listing of Later-Issued Patents

Brand-name companies may list later-issued patents (*i.e.*, patents obtained from the U.S. Patent and Trademark Office after obtaining NDA approval) so long as they do so within 30 days of being granted the patent. **Two scenarios are possible, depending on whether the**

later-issued patent is listed *prior to or after* the generic applicant files its ANDA. If the later-issued patent is listed *prior to* a generic applicant's filing of an ANDA, then the generic applicant will certify regarding that patent along with all the other listed patents. A brand name company's suit on those patents will generate only one 30-month stay, despite the fact that multiple patents are at issue in the litigation.

If, however, the **later-issued patent** is listed after a generic applicant has filed its ANDA with a paragraph IV certification, then the generic applicant must **re-certify that its ANDA does not infringe the later-issued patent. If the brand-name company sues within 45 days of the generic applicant's re-certification, then a second 30-month stay will issue.**

From this factual basis, it is quite evident that the FTC presumed that at least one patent would issue and be listed prior to an ANDA submission, and recommended a single 30-month stay to avoid a second thirty month stay caused by the listing of an additional patent after ANDA submission. To the extent that the Commission's recommendation may have been taken into account by Congress when it enacted the single 30-month stay statute, that factual basis is very different from the situation presented here, where Dey had not obtained or listed any patent prior to the filing of Ivax's ANDA.

The FTC report notes that "**even without an additional 30-month stay**, later-listed patents still receive the protections of patent infringement litigation. The brand-name company may sue for patent infringement with respect to any of its patents that it believes may be infringed by a generic applicant's ANDA..." (July 2, 2002 Study, at iv-v) (emphasis supplied). Once again, however, this observation presumes that an original 30-month stay has already issued based on a prior-listed patent, as evidenced by the highlighted language. That is not the case with Dey's '842 patent, for which the 30-month stay for which clarification is sought in this letter will be the first 30-month stay accorded.³

³ An interpretation that would deny at least one 30-month stay to Dey in this instance would also fail to take into account the extraordinary delays that commonly occur in the U.S. Patent and Trademark Office ("PTO"), thereby unnecessarily penalizing an NDA applicant who files a patent application well before an ANDA is submitted, but the patent issues after the ANDA is filed through no fault of the NDA applicant. In Dey's case, Dey diligently prosecuted the application that ultimately issued into the '842 patent, and in fact, successfully petitioned the PTO to expedite prosecution. During the course of prosecution, however, Dey still experienced unnecessary delays at the PTO.

In sum, no official from Congress, the FDA or the FTC explicitly addressed the instant scenario where an NDA applicant seeks to qualify for a single 30-month stay based on its first patent that issues and is listed after an ANDA is submitted. However, Congress was clear that the new statute codifies FDA's amended 30-month stay regulation, to which we now turn.

d. FDA's Amended 30-month Stay Regulation

As noted above, FDA's amended 30-month stay regulation, 21 C.F.R. § 314.95(a)(3), lays down the unqualified rule that there will be one 30-month stay per ANDA. But FDA did more. The agency expressly rejected the proposition that this single 30-month stay rule be restricted to patents submitted for listing prior to the submission of an ANDA. In the preamble to the final rule FDA stated:

Many comments agreed with our determination that the delay in approval of ANDA or 505(b)(2) applications could be limited to one 30-month stay per application. Other comments agreed with the limitation but stated that the single 30-month limitation was or should be:

- Per drug,
- Per ANDA, for all patents submitted before any ANDA filing, or
- Limited only to patents submitted within 30 days of NDA approval.

(Response) We decline to adopt the additional limitations as suggested by the comments. The act requires a certification for each listed patent for each application filed under sections 505(b)(2) and (j) of the act. **We construe section 505(c)(2) of the act to require submission of patent information after NDA approval, without regard to when an ANDA or 505(b)(2) application has been filed. We decline to limit the 30-month stay resulting from a paragraph IV certification to only those patents submitted before any ANDA or 505(b)(2) filing, or those filed within 30 days of ANDA approval, or per listed drug instead of per application.**

68 Fed. Reg. at 36691 (emphasis supplied).⁴

⁴ That FDA recently issued a technical amendment revoking this regulation in view of the corresponding new single 30-month stay provision in the statute does not undercut FDA's rationale for the regulation expressed in the preamble to the final rule.

The amendment to the statutory 30-month stay provision was enacted as part of the Medicare law on December 8, 2003. However, unlike most of the provisions of the amendments to Hatch-Waxman effected by the Medicare law, which became effective on the enactment date, the 30-month stay amendment was made retroactively effective to August 18, 2003, the effective date of FDA's amended regulation providing for a single 30-month stay. This is further evidence that Congress intended the new provision to be consistent with the single 30-month stay standard in the regulation.

7. Equitable Considerations Warrant Imposition of a 30-Month Stay

Dey filed its application that ultimately issued into the '842 patent in December, 2001, well before Ivax filed its ANDA in April, 2003. Dey diligently prosecuted the patent application. Due to a nearly two-year Patent Office review period beyond its control, the patent did not issue until October, 2003. The new Medicare law was enacted nearly two months after the '842 patent issued and was submitted for Orange Book listing. It would be inequitable to penalize Dey by depriving it of a single 30-month stay in these circumstances.

The primary rationale for revising the Hatch-Waxman Act was to stop gaming tactics, through important restrictions such as eliminating multiple 30-month stays and stopping inappropriate Orange Book patent listings. Certainly, Congress did not intend to stifle innovation by precluding 30-month stays to NDA applicants like Dey, who legitimately obtain and list patents in a timely manner in good faith, as opposed to intentionally late-listing patents for the sole purpose of delaying generic entry on the eve of final approval of an ANDA.

In sum, in the face of a statute that does not directly speak to the issue at hand, and legislative history that communicates Congressional intent to codify FDA's pertinent regulation, one properly turns to FDA's interpretation. That interpretation manifestly supports a single 30-month stay of approval of Ivax's ANDA based on Dey's timely-filed action for infringement of the listed '842 patent.

C. Environmental Impact

Petitioner claims a categorical exclusion from the requirement of an environmental assessment or environmental impact statement pursuant to 21 C.F.R. § 25.31.

D. Economic Impact

Pursuant to 21 C.F.R. § 10.30(b), economic impact information is to be submitted only when requested by the Commissioner following review of this Citizen Petition.

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E. Certification

The undersigned certifies that, to their best knowledge and belief, this Citizen Petition includes all information and views upon which the Petition relies, and includes representative data and information known to Petitioner which are unfavorable to the Petition.

Respectfully submitted,

DEY, L.P.

By 
Michelle A. Carpenter, J.D.
Vice President, Regulatory and Clinical
Affairs



US006632842B2

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

(10) Patent No.: **US 6,632,842 B2**
(45) Date of Patent: **Oct. 14, 2003**

- (54) **ALBUTEROL AND IPRATROPIUM INHALATION SOLUTION, SYSTEM, KIT AND METHOD FOR RELIEVING SYMPTOMS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE**
- (75) Inventors: **Imtiaz Chaudry, Napa, CA (US); Partha Banerjee, San Ramon, CA (US)**
- (73) Assignee: **Dey, L.P., Napa, CA (US)**
- (*) 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.: **10/162,460**
- (22) Filed: **Jun. 3, 2002**
- (65) **Prior Publication Data**

US 2003/0149007 A1 Aug. 7, 2003

Related U.S. Application Data

- (63) Continuation-in-part of application No. 10/034,657, filed on Dec. 28, 2001.
- (60) Provisional application No. 60/346,078, filed on Oct. 26, 2001.
- (51) Int. Cl.⁷ **A61K 31/135; A61K 9/12; A61K 31/44**
- (52) U.S. Cl. **514/651; 514/649; 514/304; 424/46; 424/45**
- (58) Field of Search **514/651, 304, 514/649; 424/46, 45**

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(List continued on next page.)

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(57) **ABSTRACT**

The present invention relates to a dual bronchodilator inhalation solution, system, kit and method for relieving bronchospasm in patients suffering from chronic obstructive pulmonary disease (COPD). In one alternative embodiment, the solution of the present invention is a prepackaged, sterile, premixed, premeasured single unit dose of albuterol and ipratropium bromide for patients suffering from COPD. The present solution may be free of antimicrobial preservatives, such as benzalkonium chloride. In another alternative embodiment, the solution of the present invention comprises about 2.50 mg albuterol and about 0.50 mg ipratropium bromide.

3 Claims, 5 Drawing Sheets-

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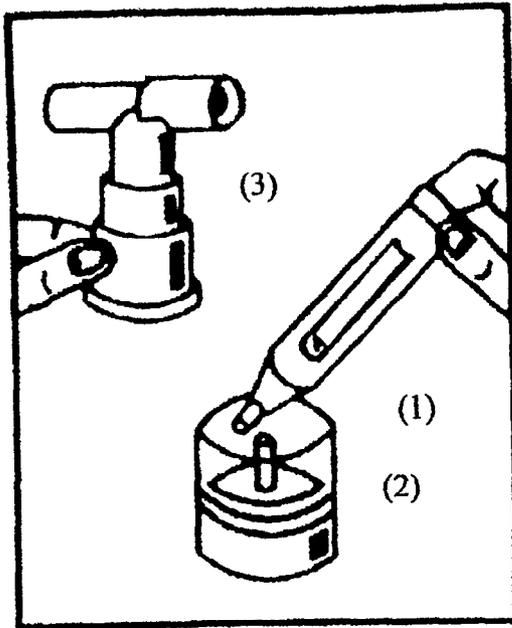


Figure 1

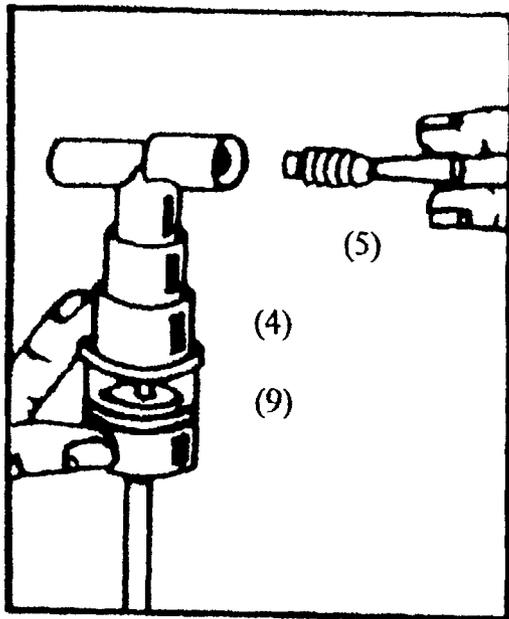


Figure 2

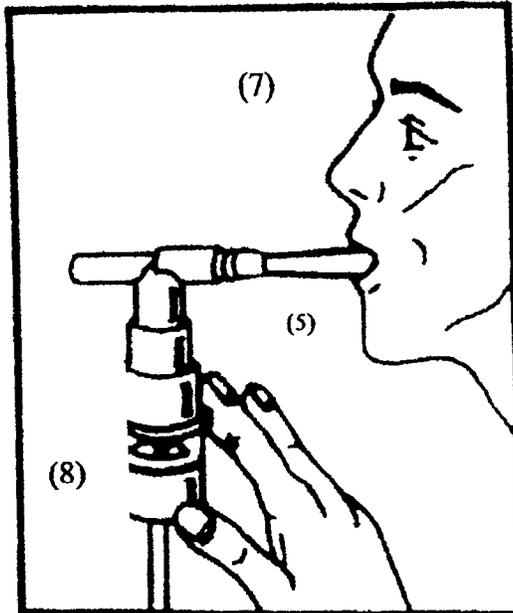


Figure 3

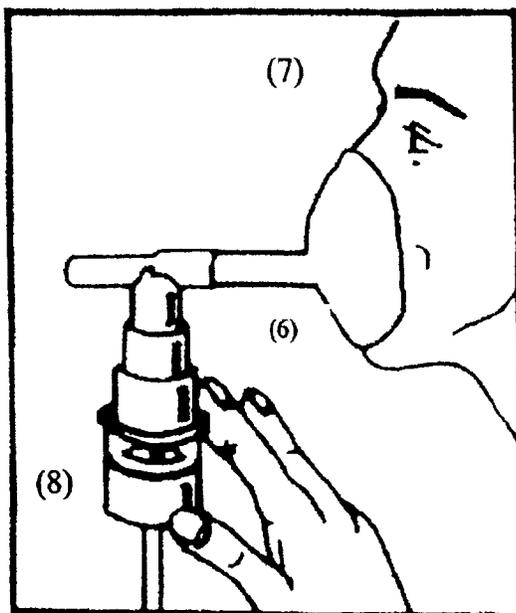


Figure 4

FIGURE 5

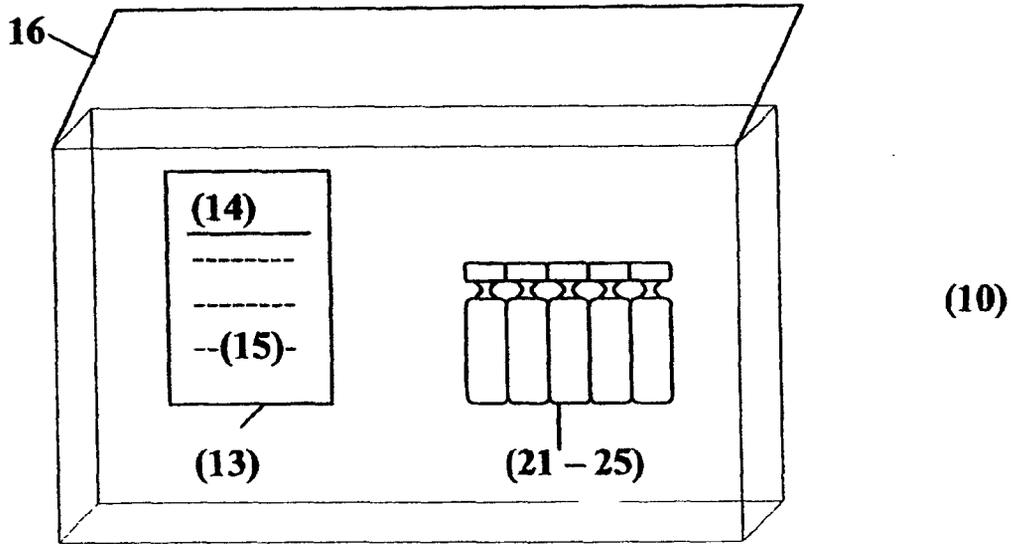


FIGURE 6

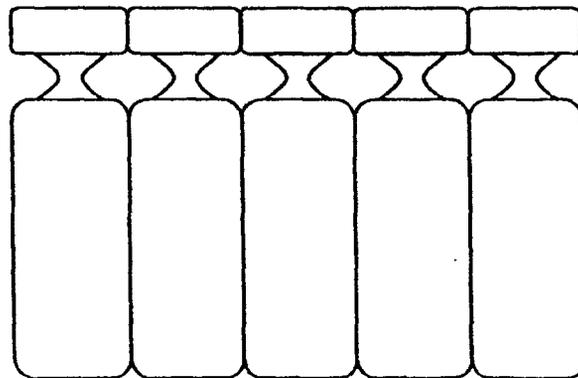
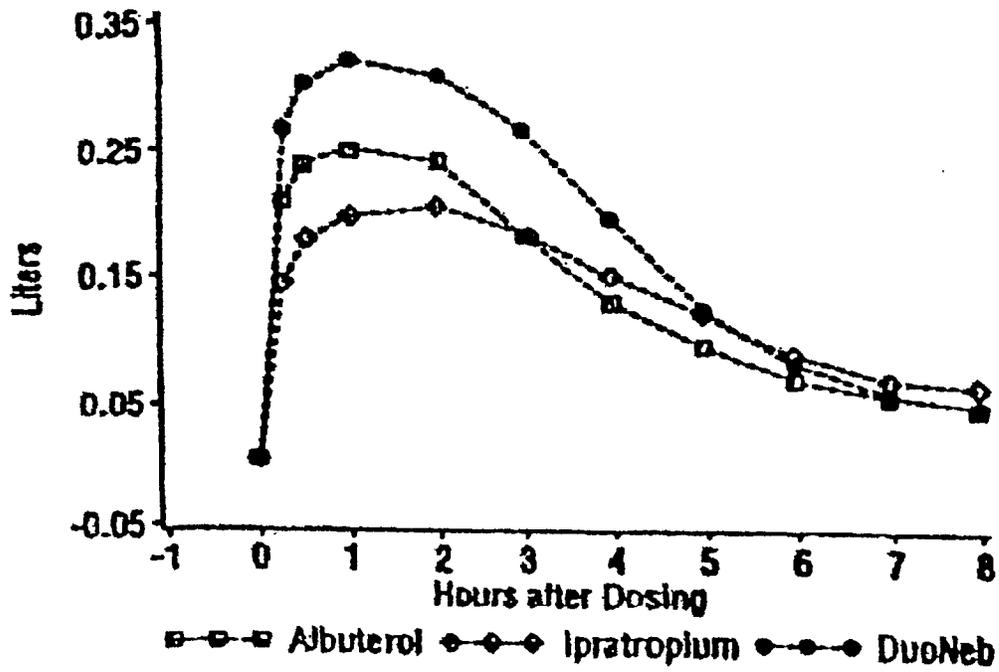


FIGURE 8

Mean change in FEV₁ - Measured on Day 14



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**ALBUTEROL AND IPRATROPIUM
INHALATION SOLUTION, SYSTEM, KIT
AND METHOD FOR RELIEVING
SYMPTOMS OF CHRONIC OBSTRUCTIVE
PULMONARY DISEASE**

**I. CROSS REFERENCE TO RELATED
APPLICATIONS**

This application is a continuation-in-part of U.S. application Ser. No. 10/034,657, filed Dec. 28, 2001, which claims priority under 35 U.S.C. §119(e) from U.S. Provisional Application Ser. No. 60/346,078, filed Oct. 26, 2001. The entire disclosure of these prior applications are incorporated herein by reference in their entirety.

II. FIELD OF THE INVENTION

The present invention relates to a combination bronchodilator therapy for relieving symptoms associated with chronic obstructive pulmonary disease.

III. BACKGROUND OF INVENTION

Chronic obstructive pulmonary disease (COPD) is a slowly progressive airway disease that produces a decline in lung function that is not fully reversible. The airway limitation in COPD is associated with an abnormal inflammatory response of the lungs to noxious particles or gases.

In the U.S., an estimated 16 million Americans have been diagnosed with some form of COPD, and as many as 16 million others have the condition but have not yet been diagnosed. According to the U.S. Centers for Disease Control and Prevention, COPD is the fourth leading cause of death in the U.S. (behind heart disease, cancer and stroke), claiming the lives of 112,000 Americans annually.

In terms of health care utilization, the number of physician visits for COPD in the U.S. increased from 9.3 million to 16 million between 1985 and 1995. The number of hospitalizations for COPD in 1995 was estimated to be 500,000. Although prevalence, hospitalization and death rates for COPD are higher in men than women, death rates have risen faster in women in recent years. COPD is clearly a major and growing health care threat in the U.S. and throughout the rest of the world.

In the prior art, antimicrobial agents such as benzalkonium chloride (BAC) are often present in inhalation solutions used to treat COPD. The presence of BAC in these solutions generally does not affect the short-term (single dose) bronchodilator response. However, case reports suggest that repeated use of COPD treatments with BAC may result in paradoxical bronchoconstriction. When inhaled by COPD subjects, BAC may also cause dose-dependent bronchoconstriction. Despite these side effects, many commercially available inhalation solutions contain BAC.

Also, treatments for COPD often come in multiple dosage units and must be diluted to specific concentrations suitable for treating patients. This poses several problems. For instance, COPD treatments requiring administration of a single dose unit from multiple dosage units sometimes lack proper mixing or diluting instructions, or the instructions for preparing and using the COPD treatment may be hard to follow or can be easily lost. Of even greater import is haphazard diluting or mixing of COPD medications, which can result in administering the wrong dosage. This could be especially harmful for patients less tolerant to higher dosages of asthma medications. Incorrect mixing can also result in treatment failure such that additional medical attention is

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required, thereby increasing the time, expense and personnel costs associated with therapy.

There is, therefore, a need for an improved inhalation solution, system, kit and method for relieving symptoms associated with COPD.

IV. SUMMARY OF THE INVENTION

One object of the present invention is to provide a dual bronchodilator inhalation solution to relieve bronchospasm in patients suffering from COPD.

Another object of the present invention is to provide a prepackaged, sterile, premixed, premeasured albuterol and ipratropium inhalation solution for the relief of bronchospasm in patients suffering from COPD.

It is yet another object of the present invention to provide a BAC-free albuterol and ipratropium inhalation solution to treat bronchospasm associated with COPD.

A further object of the present invention is to provide a method of administering an albuterol and ipratropium inhalation formulation for relief of bronchospasm associated with COPD.

An additional object of the present invention is to provide a kit and/or system for administering a dual bronchodilator to relieve bronchospasm associated with COPD.

A further object of the present invention is to provide a process for making an albuterol and ipratropium inhalation solution for use in relieving bronchospasm associated with COPD.

Another object of the invention includes a device for use in relieving the symptoms of COPD.

Other objects, features and advantages of the present invention will be apparent to those of ordinary skill in the art in view of the following detailed description of the invention and accompanying drawings.

V. BRIEF DESCRIPTION OF THE DRAWINGS

FIGS. 1-4 depict a non-limiting example of administering the inhalation solution of the present invention by a nebulizer.

FIG. 5 depicts a non-limiting example of a unified prepackaged kit or system of the present invention.

FIG. 6 depicts a non-limiting example of one or more pre-filled containers comprising the inhalation system of the present invention.

FIG. 7 depicts a non-limiting example of a label utilized in the present invention.

FIG. 8 shows the results of patients receiving the inhalation solutions of the present invention, and at least one other study medications.

**VI. DETAILED DESCRIPTION OF THE
INVENTION**

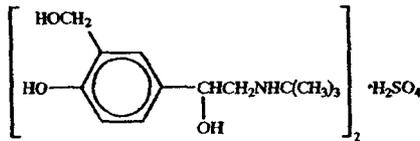
Albuterol

The present invention relies on the bronchodilation effects of albuterol to provide relief from symptoms associated with COPD. As used herein, the term "albuterol" includes, but is not limited to, any form of albuterol which is capable of producing a desired bronchodilation effect in patients, including, but not limited to, all tautomeric forms, enantiomeric forms, stereoisomers, anhydrides, acid addition salts, base salts, solvates, analogues and derivatives of albuterol.

In the present invention, acceptable salts of albuterol may include, but are not limited to, hydrochloride, sulfate,

maleate, tartrate, citrate and the like. These salts are described in U.S. Pat. No. 3,644,353, which is incorporated herein by reference in its entirety.

In the present invention, the preferred salt of albuterol is sulfate. In an alternative embodiment, the inhalation solution of the present invention comprises the sulfate salt of racemic albuterol. Albuterol sulfate is a relatively selective beta-2-adrenergic bronchodilator with an empirical formula of $C_{13}H_{21}NO_3$. The chemical name for albuterol sulfate is α^1 -[[(tert-butylamino)methyl]-4-hydroxy-m-xylene- α,α' -diol sulfate (2:1)(salt)], and its established chemical structure is as follows:

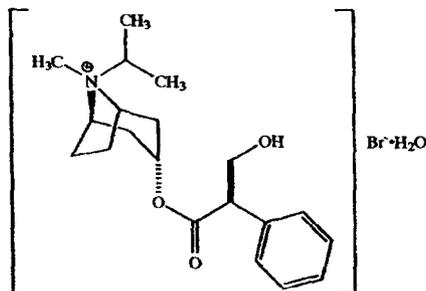


Ipratropium

The present invention also relies on the bronchodilation effect of ipratropium to provide relief from symptoms associated with COPD. Ipratropium is an anticholinergic bronchodilator. As used herein, the term "ipratropium" includes, but is not limited to, any form of ipratropium which is capable of producing a desired bronchodilation effect in patients suffering from COPD, including, but not limited to, all tautomeric forms, enantiomeric forms, stereoisomers, anhydrides, acid addition salts, base salts, salvates, analogues and derivatives of ipratropium.

In the present invention, acceptable salts of ipratropium may include, but are not limited to, halide salts such as bromide, chloride and iodide. These and other acceptable salts are described in U.S. Pat. No. 3,505,337, which is incorporated herein by reference in its entirety.

In one embodiment of the present invention, the preferred salt of ipratropium is bromide, which is chemically described as 8-azoniabicyclo[3.2.1]octane, 3-(3, hydroxyl-1-oxo-2-phenylpropoxy)-8-methyl-8-(1-methylethyl)-bromide, monohydrate, (endo, syn)-, (\pm). Ipratropium bromide has a molecular weight of 430.4 and the empirical formula $C_{20}H_{30}BrNO_3 \cdot H_2O$. It is freely soluble in water and lower alcohol, and is insoluble in lipophilic solvents such as ether, chloroform and fluorocarbon. The established chemical structure of ipratropium bromide is as follows:



In the present invention, the albuterol and ipratropium may be provided in a variety of pharmaceutically acceptable vehicles, including, but not limited to, water or other aqueous solutions comprising a pharmaceutically acceptable amount of an osmotic agent.

In one alternative embodiment, the inhalation solution of the present invention comprises a therapeutically effective

amount of albuterol and ipratropium. As used herein, the phrase "therapeutically effective amount of albuterol and/or ipratropium" means a safe and tolerable amount of both compounds, as based on industry and/or regulatory standards. Such amount being sufficient to effectively induce bronchodilation and/or provide relief of bronchospasm in patients suffering from COPD.

In the inhalation solution of the present invention, a therapeutically effective amount of albuterol may include from about 0.63 mg to about 4.2 mg albuterol. Here, the potency of the albuterol is equivalent to from about 0.75 mg to about 5 mg of albuterol sulfate. In an alternative embodiment, a therapeutically effective amount of albuterol may include about 2.5 mg albuterol.

In another alternative embodiment of the present invention, a therapeutically effective amount of albuterol may include from about 0.60 mg to about 5.0 mg albuterol, including the following intermediate ranges of albuterol: about 0.60 mg to about 0.70 mg; about 0.71 mg to about 0.80 mg; about 0.81 mg to about 0.90 mg; about 0.91 mg to about 1.00 mg; about 1.01 mg to about 1.10 mg; about 1.11 mg to about 1.20 mg; about 1.21 mg to about 1.30 mg; about 1.31 mg to about 1.40 mg; about 1.41 mg to about 1.50 mg; about 1.51 mg to about 1.60 mg; about 1.61 mg to about 1.70 mg; about 1.71 mg to about 1.80 mg; about 1.81 mg to about 1.90 mg; about 1.91 mg to about 2.00 mg; about 2.01 mg to about 2.10 mg; about 2.11 mg to about 2.20 mg; about 2.21 mg to about 2.30 mg; about 2.31 mg to about 2.40 mg; about 2.41 mg to about 2.50 mg; about 2.51 mg to about 2.60 mg; about 2.61 mg to about 2.70 mg; about 2.71 mg to about 2.80 mg; about 2.81 mg to about 2.90 mg; about 2.91 mg to about 3.00; about 3.01 to about 3.10; about 3.11 to about 3.20; about 3.21 to about 3.30 mg; about 3.31 mg to about 3.40 mg; about 3.41 mg to about 3.50 mg; about 3.51 mg to about 3.60 mg; about 3.61 to about 3.70 mg; about 3.71 to about 3.80 mg; about 3.81 mg to about 3.90 mg; about 3.91 mg to about 4.0 mg; about 4.01 mg to about 4.10 mg; about 4.11 mg to about 4.20 mg; about 4.21 mg to about 4.30 mg; about 4.31 mg to about 4.40 mg; about 4.41 mg to about 4.50 mg; about 4.51 mg to about 4.60 mg; about 4.61 mg to about 4.70 mg; about 4.71 mg to about 4.80 mg; about 4.81 mg to about 4.90 mg; about 4.91 mg to about 5.00 mg.

In another alternative embodiment of the present invention, a therapeutically effective amount of albuterol may include from about 0.75 mg to about 5.0 mg albuterol sulfate, including the following intermediate amounts: about 0.75 mg to about 0.80 mg; about 0.81 to about 0.90 mg; about 0.91 mg to about 1.00 mg; about 1.01 mg to about 1.10 mg; about 1.11 mg to about 1.20 mg; about 1.21 mg to about 1.30 mg; about 1.31 mg to about 1.40 mg; about 1.41 mg to about 1.50 mg; about 1.51 mg to about 1.60 mg; about 1.61 mg to about 1.70 mg; about 1.71 mg to about 1.80 mg; about 1.81 mg to about 1.90 mg; about 1.91 mg to about 2.00 mg; about 2.01 mg to about 2.10 mg; about 2.11 mg to about 2.20 mg; about 2.21 mg to about 2.30 mg; about 2.31 mg to about 2.40 mg; about 2.41 mg to about 2.50 mg; about 2.51 mg to about 2.60 mg; about 2.61 mg to about 2.70 mg; about 2.71 mg to about 2.80 mg; about 2.81 mg to about 2.90 mg; about 2.91 mg to about 3.00; about 3.01 to about 3.10; about 3.11 to about 3.20; about 3.21 to about 3.30 mg; about 3.31 mg to about 3.40 mg; about 3.41 mg to about 3.50 mg; about 3.51 mg to about 3.60 mg; about 3.61 to about 3.70 mg; about 3.71 to about 3.80 mg; about 3.81 mg to about 3.90 mg; about 3.91 mg to about 4.0 mg; about 4.01 mg to about 4.10 mg; about 4.11 mg to about 4.20 mg; about 4.21 mg to

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about 4.30 mg; about 4.31 mg to about 4.40 mg; about 4.41 mg to about 4.50 mg; about 4.51 mg to about 4.60 mg; about 4.61 mg to about 4.70 mg; about 4.71 mg to about 4.80 mg; about 4.81 mg to about 4.90 mg; about 4.91 mg to about 5.00 mg.

In another alternative embodiment of the present invention, a therapeutically effective amount of albuterol may include from about 0.020% to about 0.14% by weight albuterol, including the following intermediate ranges: about 0.020 wt % to about 0.029 wt %; about 0.030 wt % to about 0.039 wt %; about 0.040 wt % to about 0.049 wt %; about 0.050 wt % to about 0.059 wt %; about 0.060 wt % to about 0.069 wt %; about 0.070 wt % to about 0.079 wt %; about 0.080 wt % to about 0.089 wt %; about 0.090 wt % to about 0.099 wt %; about 0.10 wt % to about 0.14 wt %.

In yet another alternative embodiment of the present invention a therapeutically effective amount of albuterol may include from about 0.025% to about 0.17% by weight albuterol sulfate, including the following intermediate ranges: about 0.025 wt % to about 0.029 wt %; about 0.030 wt % to about 0.039 wt %; about 0.040 wt % to about 0.049 wt %; about 0.050 wt % to about 0.059 wt %; about 0.060 wt % to about 0.069 wt %; about 0.070 wt % to about 0.079 wt %; about 0.080 wt % to about 0.089 wt %; about 0.090 wt % to about 0.099 wt %; about 0.10 wt % to about 0.17 wt %.

In another alternative embodiment of the present invention a therapeutically effective amount of ipratropium bromide may include from about 0.01 mg to about 1.0 mg of ipratropium bromide. Such therapeutically effective amount may also include the following intermediate ranges of ipratropium bromide: about 0.01 mg to about 0.02 mg; about 0.02 mg to about 0.04 mg; about 0.05 to about 0.07 mg; about 0.08 mg to about 0.10 mg; about 0.11 mg to about 0.13 mg; about 0.14 mg to about 0.16 mg; about 0.17 mg to about 0.19 mg; about 0.20 mg to about 0.22 mg; 0.23 mg to about 0.25 mg; 0.26 mg to about 0.28 mg; about 0.29 mg to about 0.31 mg; about 0.32 to about 0.34 mg; about 0.35 mg to about 0.37 mg; about 0.36 mg about 0.38 mg; about 0.39 mg to about 0.41 mg; about 0.42 mg to about 0.44 mg; about 0.45 mg to about 0.47 mg; about 0.48 mg to about 0.50 mg; about 0.51 mg to about 0.53 mg; about 0.54 mg to about 0.56 mg; about 0.57 mg to about 0.59 mg; about 0.60 mg to about 0.62 mg; about 0.63 mg to about 0.65 mg; about 0.66 mg to about 0.68 mg; about 0.69 mg to about 0.71 mg; about 0.72 mg to about 0.74 mg; about 0.75 mg to about 0.77 mg; about 0.79 mg to about 0.81 mg; about 0.82 mg to about 0.84 mg; about 0.85 mg to about 0.87 mg; about 0.88 mg to about 0.91 mg; about 0.92 mg to about 0.94 mg; about 0.95 mg to about 0.97 mg; about 0.98 mg to about 1.00 mg.

In another alternative embodiment of the present invention, a therapeutically effective amount of ipratropium may include from about 0.001% to about 0.030% by weight ipratropium bromide, including the following intermediate ranges of ipratropium bromide: about 0.001 wt % to about 0.005 wt %; about 0.006 wt % to about 0.010 wt %; about 0.011 wt % to about 0.015 wt %; about 0.016 wt % to about 0.020 wt %; about 0.021 wt % to about 0.025 wt %; 0.026 wt % to about 0.030 wt %.

Most pharmaceutical inhalation solutions contain the antimicrobial agent BAC. One problem with these solutions is that the BAC may cause paradoxical bronchoconstriction if the solution is administered repeatedly over short intervals. Another problem is that, when inhaled by patients, the BAC can cause dose-dependent bronchoconstriction. The inhalation solution of the present invention may be provided

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without BAC, thereby making it suitable, especially in an emergency situation, where the inhalation solution is administered repeatedly over a short period of time. Also, administering a BAC-free inhalation solution to a patient reduces the concomitant liability of adverse effects associated with BAC. It also reduces the toxicity and other side effects associated with BAC.

The inhalation solution of the present invention may also be provided in sterile, unit dose treatments, thus eliminating the need to include BAC in the solution. Moreover, as shown in Table 1, in its sterile form the formulation of the present invention (which comprises a therapeutically effective amount of albuterol sulfate and ipratropium bromide) provides a stable inhalation solution such that the formulation can be stored (e.g., on a shelf) for long periods of time.

TABLE 1

Stability Data					
0.083 wt % Albuterol Sulfate and 0.017 wt % Ipratropium Bromide					
Assay*					
		Albuterol sulfate	Ipratropium bromide	pH	Osmolality (mOsm/kg)
	Time zero	98	98	3.3	283
	25° C./ 12 months	105	99	3.4	285
	35% RH 24 months	102	101	3.5	282
	40° C./ 3 months	100	99	3.5	284
	15% RH 6 months	103	102	3.4	283

*as percent of label claim (0.083 wt % albuterol sulfate and 0.017 wt % ipratropium bromide)

As stated, the compositions provided herein are stable. For example, the compositions provided herein are stored between about 15° C. and about 30° C., and remain stable for a relatively long period of time. In one embodiment, the compositions are stored at 25° C.

In another embodiment, the stability of the compositions provided herein may contain greater than 80%, 85%, 90% or 95% of the initial amount of active ingredient, e.g., Albuterol and Ipratropium at a given temperature for a long period of time. Thus, for example, a composition that is stable for 30 days at 25° C. would have greater than 80%, 85%, 90% or 95% of the initial amount of active ingredients present in the composition at 30 days following storage at 25° C.

In another embodiment, the compositions herein are stable during long term storage, in that the compositions are suitable for administration to a subject in need thereof when they have been stored for a length of time (i.e., shelf-life) for a period greater than 1, 2 or 3 years at 25° C. In other embodiments herein, using Arrhenius Kinetics, >80% or >85% or >90% or >95% estimated bronchodilating agent remains after such storage, for example.

Other indications of the stability of the present compositions can be shown in terms of by-products or degradation products present over time, as shown in Tables 2 and 3 below.

TABLE 2

Albuterol degradation products/related compounds as % of albuterol	Range at 6 to 24 months at 25° C.	Range in drug substance
1 5-2-((1,1-Dimethylethyl)amino-1-hydroxyethyl)-2-hydroxybenzaldehyde	ND-0.012% w/w	
2 Bis-(2-hydroxy-5-(2-tertbutylamino-1-hydroxyethyl) phenylmethyl ether		0.09-0.174% w/w
3 2-tert-butylamino-1-(4-hydroxy-3-methoxymethylphenyl)-ethanol		0.01-0.12% w/w
4 Tert-butylamino-3-chloro-4-hydroxy-5-hydroxymethylacetophenone		ND-0.0002% w/w
5 Tert-butylamino-4-hydroxy-5-hydroxymethylacetophenone		ND-0.002% w/w
6 1-(4-hydroxy-3-methylphenyl)-2-(tert-butylamino) ethanol		0.0009-0.036% w/w
7 1-(5-chloro-4-hydroxy-3-hydroxymethylphenyl)-2-(tert-butylamino) ethanol		ND
8 Unknown 1	ND-0.07% by peak area	
9 Any other unknown	ND-0.025% by peak area	
10 Total	0.18-0.23%	

ND = none detected

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TABLE 3

Ipratropium degradation products/related compounds as % of ipratropium bromide	Range at up to 24 months at 25° C.	Range in drug substance
1 Tropic acid	ND-0.08% w/w	
2 8S-ipratropium bromide		ND-0.058% w/w
3 N-isopropyl-noratropine		ND
4 Ipratropium alcohol	ND-0.038% w/w	
5 Any other unknown	ND	
6 Atropic acid	ND	
7 Total (excluding APO-ipratropium)	ND-0.2%	

ND = none detected

In one embodiment, the compositions herein are at least substantially clear, based on color measurement tests set forth by the American Public Health Association ("APHA"). In another embodiment of the present invention, the APHA color results for compositions herein at upto 24 months at 25° C. ranged from 0 to 5 units (mostly 0 units), as based on APHA standards.

In one embodiment, the process of the present invention provides compositions having an albuterol content of about 2.5 mg to about 2.75 mg per vial. In another alternative embodiment, the process of the present invention provides compositions having an Ipratropium content of about 0.45-0.55 mg per vial. In yet another alternative embodiment, the process of the present invention provides an average fill volume of about 2.84 to about 3.30 ml into each vial.

In another alternative embodiment, the compositions of the present invention may contain minimal amounts of contaminants including, but not limited to the following:

TABLE 4

	1. Volatiles	
30	acetone	about NMT 0.2 Φg/ml or less
	ethyl acetate	about NMT 0.3 Φg/ml or less
	n-heptane	NMT 0.1 Φg/ml or less
	n-propylacetate	NMT 0.3 Φg/ml or less
	toluene	NMT 0.3 Φg/ml or less
	2-butanone	none detected (signal/noise NMT 3)
	unknowns	
35	2. Leachables	
	Irganox 129	none detect (NMT 0.02 Φg/ml)
	Extractable 1	none detected (signal/noise NMT 3)
	Extractable 2	none detected (signal/noise NMT 3)
	unknowns	none detected (signal/noise NMT 3)
40		

In another alternative embodiment, compositions of the present invention may contain minimal amounts of particulate matter, including, but not limited to the following: NMT about 1000 to 5000, preferably about 3800 particles/vial>2Φm; NMT about 10 to 100, preferably about 80 particles/vial>10Φm; or NMT about 1 to 5, preferably about 3 particles/vial>25Φm.

Another benefit of a sterile inhalation solution is that it reduces the possibility of introducing contaminants into the patient when administered, thereby reducing the chance of an opportunistic infection in the patient.

Non-adherence to COPD medication therapy and medication error are considerable problems. These problems can be significantly reduced by providing COPD patients a prepackaged, premixed, premeasured amount of albuterol and ipratropium. Providing these compounds in this fashion makes COPD therapy simple because it increases convenience and eliminates confusion in preparing appropriate dosages. These advantages are especially significant where treatments often come in multiple dosage units and must be diluted to specific concentrations suitable for treating patients. As discussed previously, this poses several problems.

The present invention overcomes the aforementioned problems by providing therapeutically effective amounts of both albuterol and ipratropium in prepackaged, premixed,

premeasured and/or unit dose amounts. In one embodiment, the present invention comprises one or more prefilled containers. The one or more containers each comprising a single unit dose of an aqueous solution comprising a therapeutically effective amount of albuterol and ipratropium for the treatment of COPD. Providing the inhalation solution in such a manner eliminates the need to dilute or mix COPD medications to obtain proper dosages for treatment. Also, no special pharmacy compounding is required, thereby reducing the chance of medication errors. Further, there is a lower risk of cross-contamination, and less waste of medication when providing an inhalation solution in a premixed, ready to use form.

Other features of the present invention include improved user compliance and quality of life as compared to conventional treatments for COPD. While the level of compliance of any COPD treatment depends in part on the motivation of the user and the skill of the individual dispensing the treatment, compliance nevertheless may be improved by controlling factors such as the ease with which the treatment may be administered, as well as the desirability of receiving the treatment.

The present invention provides a convenient, fast and reliable treatment for COPD and clearly represents an improvement over traditional COPD treatments. Also, the present invention is designed to facilitate user compliance by providing one or more dispensing containers comprising a premixed, premeasured inhalation solution comprising a single unit dose of a therapeutically effective amount of albuterol and ipratropium for the treatment of COPD. Such containers may be utilized in a method of treating COPD or the containers may be incorporated in a system and/or kit for treating the same.

In one alternative embodiment, the present invention is a sterile, premixed, premeasured, BAC-free inhalation solution comprising a single unit dose of a therapeutically effective amount of albuterol and ipratropium in a single container. Each unit dose container comprises 3.0 mg/3 ml of albuterol sulfate (equivalent to 2.5 mg of albuterol) and 0.5 mg ipratropium bromide in a sterile, aqueous solution. Sodium chloride may be added to make the solution isotonic and hydrochloric acid may be added to adjust pH of the solution to about 4.0. The inhalation solution of the present invention may or may not include a chelating agent, such as EDTA.

In another alternative embodiment, the inhalation solution of the present invention may be supplied as a 3 ml, sterile, BAC-free, nebulizer solution comprising from about 0.20 to about 0.5 mg ipratropium bromide and from about 0.75 mg/3 ml to about 3.0 mg/3 ml of albuterol sulfate. The nebulizer solution is contained in a unit-dose, low-density polyethylene (LDPE) container. Each unit-dose container may be disposed in a foil pouch, and each foil pouch may contain 5 or more unit-dose containers. Each foil pouch containing the unit dose container may be disposed in a shelf carton.

The present invention provides an albuterol and ipratropium inhalation solution for treating different stages of COPD, including but not limited to, stages 0 to III. Some characteristics associated with the different stages of COPD are shown in Table 2. The information in this table is presented for illustrative purposes only. It is not intended to limit the scope of the invention.

TABLE 2

Stage	Severity	Description
0	At risk	•Normal spirometry •Chronic symptoms (cough, sputum production)
I	Mild	•FEV ₁ /FVC < 70% •FEV ₁ > 80% predicted •With or without chronic symptoms
II	Moderate	•FEV ₁ /FVC < 70% •30% ≥ FEV ₁ < 80% predicted (IIA: 50% ≥ FEV ₁ < 80%) (IIB: 30% ≥ FEV ₁ < 50%) •With or without chronic symptoms
III	Severe	•FEV ₁ /FVC < 70% •FEV ₁ < 30% predicted or less than 50% predicted with respiratory failure or clinical signs of right heart failure.

In the present invention, a therapeutically effective amount of albuterol and ipratropium is administered to induce bronchodilation and/or provide relief of bronchospasm associated with COPD. Such amount of albuterol and ipratropium may be administered to a patient after the onset of bronchospasm to reduce breathing difficulties resulting from COPD. In another embodiment, the albuterol and ipratropium may be administered prophylactically, that is, to prevent COPD progression.

The quantity of albuterol and ipratropium to be administered will be determined on an individual basis, and will be based at least in part on consideration of the patient's size, the severity of the symptoms to be treated, and the results sought. The actual dosage (quantity of albuterol and ipratropium administered at a time) and the number of administrations per day will depend on the mode of administration, such as inhaler, nebulizer or oral administration. For example, about 2.5 mg of albuterol and about 0.5 mg of ipratropium bromide administered by nebulization 4 times per day with up to 2 additional 3 ml doses allowed per day, if needed, would be adequate to produce the desired bronchodilation effect in most patients.

Further, the albuterol and ipratropium inhalation solution of the present invention may be administered together with one or more other drugs. For example, an antiasthmatic drug such as theophylline or terbutaline, or an antihistamine or analgesic such as aspirin, acetaminophen or ibuprofen, may be administered with or in dose temporal proximity to administration of a therapeutically effective amount of albuterol. The present invention and the one or more drugs may be administered in one formulation or as two separate entities. According to the present invention, a therapeutically effective amount of albuterol and ipratropium, alone or in combination with another drug(s), may be administered to an individual periodically as necessary to reduce symptoms of COPD.

In another alternative embodiment, the inhalation solution of the present invention may be administered by nebulizer. Such nebulizer including, but not limited to, a jet nebulizer, ultrasonic nebulizer and breath actuated nebulizer. Preferably, the nebulizer is a jet nebulizer connected to an air compressor with adequate air flow. The nebulizer being equipped with a mouthpiece or suitable face mask. Specifically, a Pari-LC-Plus™ nebulizer (with face mask or mouthpiece) connected to a PRONEB™ compressor may be used to deliver the inhalation solution of the present invention to a patient.

In an alternative embodiment, the system and/or kit of the present invention comprises an inhalation solution compris-

ing a therapeutically effective amount of albuterol and ipratropium in a prepackaged, premeasured, premixed and/or single unit dose form for the treatment of COPD. The inhalation solution may be sterile and/or BAC-free.

In another embodiment, the present invention provides a system and/or kit for organizing and storing one or more pre-filled dispensing containers, each container comprising a premixed, premeasured inhalation solution. The inhalation solution comprising a single unit dose of a therapeutically effective amount of albuterol and ipratropium. Such system and/or kit may provide such containers in prepackaged form. The one or more containers may be comprised of plastic including, but not limited to, a semi-permeable plastic such as LDPE. The container may also comprise a Twist-Flex™ top, such top comprising an easy-to-grip tab-like handle such that the container may be opened, for example, by twisting off the tab by hand. The Twist-Flex™ top is advantageous in that it allows for easy dispensing of the solution, prevents spillage and eliminates the need to open the container by cutting off the top, or the like, thereby reducing cross-contamination. One or more of the semi-permeable single unit dose containers may be prepackaged in an aluminum foil pouch, such that the foil provides a protective barrier against environmental contaminants and light. Such a barrier improves the shelf-life and stability of the inhalation solution.

In another alternative embodiment, the present invention comprises a prepackaged inhalation system and/or kit suitable for patients suffering from COPD. Such prepackaged system and/or kit comprising: (a) one or more single unit dosages of a therapeutically effective amount of albuterol and ipratropium; (b) administration instructions for the use of said unit dose as a treatment for COPD; and (c) a dispensing container pre-filled with the one or more unit doses of albuterol and ipratropium.

In another alternative embodiment, the prepackaged inhalation system and/or kit of the present invention provides one or more premixed, premeasured single unit dose vials comprising a therapeutically effective amount of albuterol and ipratropium for the treatment of bronchospasm associated with COPD, and instructions for using the same.

The prepackaged inhalation system and/or kit may be provided in one of any number of forms, including, but not limited to, a box containing one or more prepackaged, unit dose vials or a box containing individual packages or pouches comprising one or more unit dose vials. For example, an embodiment of a unified prepackaged system and/or kit for treating COPD in patients is depicted in FIG. 5. Specifically, FIG. 5 depicts support package (10). Support package (10) may include, but is not limited to, a box, carton or any other enclosed container. The support package comprising one or more prepackaged, pre-filled dispensing containers (21-25). Each container comprising a premixed, premeasured inhalation solution. The inhalation solution comprising a unit dose of a therapeutically effective amount of albuterol and ipratropium for treating COPD. The inhalation solution may be provided in sterile and/or BAC-free form.

Support package (10) may also incorporate one or more labels (13) therein. One or more labels (13) may comprise indicia (14) indicating that the inhalation solution can be used to relieve symptoms associated with COPD, such as bronchospasm. The label may also comprise indicia (15) which provides instructions for using the inhalation solution to relieve such symptoms. As used herein "indicia" includes, but is not limited to, wording, pictures, drawings, symbols

and/or shapes. A non-limiting example of the indicia that may appear on the one or more labels (13) is shown in FIG. 7. The one or more labels may be positioned on one or more surfaces of support package (10) or a separate sheet, or any combination thereof. Support package (10) may also incorporate lid (16) to enclose the packaging material therein.

The system and/or kit of the present invention may also include a label and/or instructions designed to facilitate user compliance. For example, in an embodiment, a system and/or kit of the present invention comprises packaging material containing one or more prepackaged vials comprising a sterile, premixed, premeasured unit dose of an inhalation solution comprising a therapeutic effective amount of albuterol and ipratropium. The packaging material may further comprise a label indicating that each vial can be used with a nebulizer for the relief of symptoms associated with COPD, such as bronchospasm. Such instructions may also include instructions on dosage for each nebulizer treatment, as well as instructions for administration, such as by nebulizer. The instructions may be positioned on one or more surfaces of the packaging material therein, or the instructions may be provided on a separate sheet, or any combination thereof.

The present invention is also directed to a method of treating symptoms associated with COPD, including bronchospasm, wherein a therapeutically effective amount of albuterol and ipratropium may be administered as a unit dose. Such unit dose may be in the form of a nebulizer solution.

In an alternative embodiment, the method of the present invention comprises the step of administering to a patient a therapeutically effective amount of albuterol and ipratropium. Such solution may also be prepackaged, premixed, premeasured, BAC-free and/or sterile. Such solution may also be in a single unit dose vial.

In another alternative embodiment, the method of the present invention comprises the step of administering to a patient in need an inhalation solution comprising a therapeutically effective amount of albuterol and ipratropium. The inhalation solution being administered by nebulizer, more preferably a jet nebulizer connected to an air compressor with adequate air flow.

In yet another alternative embodiment, in reference to FIGS. 1-4, the method of the present invention comprises the steps: (i) placing an inhalation solution comprising a therapeutically effective amount of albuterol and ipratropium (1) into a nebulizer cup (2). The nebulizer may be powered by attachment to compressed gas cylinders or an electrically driven compressor; (ii) using a "T" adapter (3) to fit the nebulizer cup lid (4) to a mouthpiece (5) or facemask (6); (iii) drawing the inhalation solution (1) up by the velocity of a gas jet and fragmenting it into an aerosol; (iv) passing the aerosol through the mouthpiece (5) or facemask (6) to the patient (7) afflicted with bronchospasm; and (v) the patient continues breathing until no more mist is formed in the nebulizer chamber (8). This may occur in about 5-15 minutes.

In one alternative embodiment, the usual starting dosage for patients may be about 2.50 mg albuterol and 0.5 mg ipratropium administered 3 or 4 times daily, as needed by nebulization. To administer these amounts of albuterol and ipratropium, the entire contents of one unit dose vial (e.g., about 3.0 mg/3 ml albuterol sulfate and 0.5 mg/3 ml ipratropium bromide) may be used. Preferably, the nebulizer flow rate is adjusted to deliver the albuterol and ipratropium over 5 to 15 minutes.

Further, in an alternative embodiment, the method of the present invention comprises the steps: (i) preparing an inhalation solution comprising a therapeutically effective amount of albuterol and ipratropium by diluting one or more solutions comprising the ipratropium or albuterol; and (ii) administering the inhalation solution to a patient in need thereof.

The present invention also provides a process for making a prepackaged, sterile, premixed, premeasured, and/or BAC-free inhalation solution comprising a single unit dose of a therapeutically effective amount of albuterol and ipratropium. In such an embodiment, the method of the present invention comprises one or more of the following steps: (i) adding at least a therapeutically effective amount of albuterol and ipratropium in a carrier, such as water; (ii) sterilizing the solution and sealing the container. An osmotic adjusting agent may be added to adjust the isotonicity of the solution. Preferably, the solution of the present invention is isotonic, and an osmotic adjusting agent may be added to adjust the isotonicity of the solution to about 280 to about 320 mOsm/kg. Additionally, an acid (e.g., hydrochloride) may be added to adjust the pH of the solution to a level of about 3.0 to about 5.0, preferably about 4.0.

In another embodiment, a process for making an inhalation solution of the present invention comprises one or more of the following steps: (i) adding at least a therapeutically effective amount of albuterol and ipratropium in a carrier such as water; (ii) placing the mixture in a container, and sterilizing the mixture by steam sterilization, or any other sterilizing means known in the art. Each albuterol and ipratropium mixture being filled into a vial, and then packaged, stored and/or used directly. Here, the resulting mixture is stable, and after sterilization, it can be dispersed, if necessary, into multiple mixtures each containing a unit dose of a therapeutically effective amount of albuterol and ipratropium.

Osmotic adjusting agents which may be used include, but are not limited to, sodium chloride, potassium chloride, zinc chloride, calcium chloride and mixtures thereof. Other osmotic adjusting agents may also include, but are not limited to, mannitol, glycerol, and dextrose and mixtures thereof. In an alternative embodiment, the present invention may comprise about 0.4 to about 1.0 weight percent ionic salt. Preferably, the present invention comprises 0.9 wt % of an osmotic adjusting agent.

In an alternative embodiment, the inhalation solution of the present invention may be prepared as follows: (i) fitting a stainless steel formulation tank with a bottom drain and a tri-blender for mixing; (ii) filling the tank with approximately 95% of the required amount of Purified Water USP at a temperature of between 18° C. to 25° C.; while mixing, (iii) adding EDTA USP, hydrochloric acid, and at least a therapeutically effective amount of Albuterol Sulfate USP and Ipratropium Bromide to the tank; (iv) continue mixing until all chemical components are dissolved; (v) adding Purified Water USP to adjust the final volume, if necessary, thus producing an albuterol and ipratropium bromide mixture.

From the formulation tank, the albuterol and ipratropium mixture is pumped through sanitary delivery lines directly into a form-fill-seal (FFS) machine. The albuterol and ipratropium mixture passes through a 0.2 micron sterilizing cartridge filter, then into a reservoir tank, through a second 0.2 micron sterilizing cartridge filter to the filling nozzles within the sterile air shower compartment, and subsequently into formed vials of low density polyethylene (LDPE). The

albuterol and ipratropium mixture being sterile filled into the vials such that each vial contains a single unit dose of a therapeutically effective amount of albuterol. The filled vials are then sealed. The FFS machine may form, fill and seal the vials in a continuous operation under aseptic conditions, thus producing a sterile product. For example, cards of five filled vials (FIG. 6) may be overwrapped into a protective laminated foil pouch using an autowrapper machine. Six to twelve such pouches may then be packaged in a shelf carton, thus forming a prepackaged therapeutic system for treating COPD in patients. An appropriate label and instructions may be added in the shelf carton.

The present invention is also directed to a method of forming a unit-dose nebulizer solution comprising the step of: (i) preparing a mixture containing a therapeutically effective amount of albuterol and ipratropium bromide in a pharmaceutically acceptable carrier. Said mixture being suitable for nebulization in a nebulizer.

In an alternative embodiment, the present invention also comprises a device for use in the relief of symptoms associated with COPD, including bronchospasm. Such device may take the form of a label, written instructions or any other form incorporating indicia thereon. The device may comprise indicia which indicates that a patient suffering from symptoms associated with COPD can be treated with at least one prepackaged, sterile, premixed, premeasured and/or BAC-free inhalation solution comprising a unit dose of a therapeutically effective amount of albuterol and ipratropium in a single vial. The inhalation solution being suitable for nebulization in a nebulizer. The device may also comprise indicia which provides instructions for utilizing the inhalation solution to treat said symptoms in patients.

EXAMPLES

To evaluate the efficacy and safety of the inhalation solution of the present invention, a double-blind, randomized, positive control trial was performed. The design, results and conclusion of the study are described in detail below.

Patients

A total of 863 patients were initially randomized for enrollment in the trial. To be eligible for enrollment, patients had to meet the criteria described in Table 3.

TABLE 3

Inclusion/Exclusion Criteria	
Design Element	Description
Inclusion Criteria	<ul style="list-style-type: none"> *Diagnosis with COPD with an FEV₁ between 25% and 65% of the normal predicted value. *Age > 40 years. *Regular use of one or more bronchodilators for a minimum of 3 months prior to enrollment. *History of at least 10 pack-years of smoking. *Ability to refrain from the use of theophylline, salmeterol and oral β_2 agonists for the duration of the trial (as judged by the investigator). *Ability to safely complete a 6-minute walk. *Willingness to provide informed consent.
Exclusion Criteria	<ul style="list-style-type: none"> *Diagnosis of anthracosis, silicosis, any parenchymal disease not attributable to COPD, polycythemia, or pulmonale, hypoxia, or a primary diagnosis attributable to allergic rhinitis, atopy, or COPD. *Clinically significant obstructive urinary disease, narrow-angle glaucoma, unstable angina pectoris or myocardial infarction in the past 6 months, known drug abuse within

TABLE 3-continued

Inclusion/Exclusion Criteria	
Design Element	Description
	the last 12 months, or hospitalization for pulmonary exacerbation within the past 2 months.
	*Known hypersensitivity to any component of the study medications.
	*Investigational drug use within 30 days of first dose of study medication.
	*Pregnancy or breastfeeding.

Interventions

The doses of each individual agent and the ipratropium and albuterol combination were as shown in Table 4 below. All study medications were administered 4 times per day (ideally every 6 hours) by inhalation using a Pari LC Plus™ nebulizer and Pari Proneb™ compressor. Concomitant use of bronchodilators was restricted during the trial. Oral and inhaled steroid use was permitted throughout the trial, provided that dosing remained constant.

TABLE 4

Study Medication	Albuterol (base)	Ipratropium bromide
Albuterol alone	2.5 mg	
Ipratropium alone		0.5 mg
Albuterol and Ipratropium Combination	2.5 mg	0.5 mg

Efficacy Results

Of the 863 patients who were randomized and began treatment, 289 withdrew prematurely from the trial, including 28 patients who did not meet the inclusion/exclusion criteria and were inappropriately enrolled. A total of 663 patients received both the inhalation solution of the present invention and at least one other study medication and completed at least one post-dose measurement of FEV₁. These subjects contributed to the 647 evaluable comparisons in each portion of the primary analysis, as the majority of patients completed treatment on all three study medications.

The primary efficacy variable was the change from pre-dose to peak FEV₁ measured within 3 hours after dosing during the crossover phase of the trial. As can be seen in Table 5, the mean increase in FEV₁ was significantly higher for the albuterol and ipratropium combination than for either agent used alone. The improvement for the combination over albuterol alone was 23.6% and over ipratropium alone was 37.2%. The time course of FEV₁ response is shown in FIG. 8.

TABLE 5

Parameter	Efficacy Results in Crossover Phase				n	Efficacy Results in Crossover Phase			
	Combination vs. Albuterol					Combination vs. Ipratropium			
	n	Combination mean	Albuterol mean	p value		n	Combination mean	Ipratropium mean	p value
Peak FEV ₁ (liters)	647	0.387	0.313	<0.001	647	0.387	0.282	<0.001	

During the parallel phase of the trial, separate groups of patients self-administered only one of the three study medi-

cations during the final 6 weeks of the trial. Results for the parallel phase yielded results essentially identical to the crossover phase. The albuterol and ipratropium combination maintained the same magnitude of superiority over each component medication alone that was observed during the crossover phase in peak FEV₁ response.

Safety/Tolerability

Adverse reactions concerning the albuterol and ipratropium combination were evaluated from the clinical trials described above. Treatment-emergent adverse events that were reported by 1% or greater of patients are summarized by medication in Table 6. As can be seen, there were no differences between the albuterol and ipratropium combination and the individual medication in incidence of patients with adverse events across body systems.

TABLE 6

Adverse Event Reports
(ADVERSE EVENTS OCCURRING IN > 1% OF TREATMENT GROUP(S) AND WHERE THE COMBINATION TREATMENT SHOWED THE HIGHEST PERCENTAGE)

Body System	Albuterol n (%)	Ipratropium n (%)	Albuterol and Ipratropium Combination n (%)
COASTART Term			
NUMBER OF PATIENTS	761	754	765
N (%) Patients with A BODY AS A WHOLE	327 (43.0)	329 (43.6)	367 (48.0)
Pain			
Pain chest	8 (1.1)	4 (0.5)	10 (1.3)
11 (1.4)	14 (1.9)	20 (2.6)	
DIGESTIVE			
Diarrhea	5 (0.7)	9 (1.2)	14 (1.8)
Dyspepsia	7 (0.9)	8 (1.1)	10 (1.3)
Nausea	7 (0.9)	6 (0.8)	11 (1.4)
MUSCULO-SKELETAL			
Cramps leg	8 (1.1)	6 (0.8)	11 (1.4)
RESPIRATORY			
Bronchitis	11 (1.4)	13 (1.7)	13 (1.7)
Lung Disease	36 (4.7)	34 (4.5)	49 (6.4)
Pharyngitis	27 (3.5)	27 (3.6)	34 (4.4)
Pneumonia	7 (0.9)	8 (1.1)	10 (1.3)
UROGENITAL			
Infection urinary tract	3 (0.4)	9 (1.2)	12 (1.6)

Additional adverse reactions reported in more than 1% of patients treated with the albuterol and ipratropium combination included constipation and voice alterations.

The figures and attachments herein are presented for illustrative purposes only. They are not intended to limit the scope of the invention. Further, it should be understood that various changes and modifications to the presently preferred

embodiment described herein will be apparent to those skilled in the art. Such changes and modifications can be

made without departing from the spirit and scope of the present invention and without diminishing its attendant advantages. It is therefore intended that such changes and modifications be covered by the appended claims.

Also, the invention may suitably comprise, consist of or consist essentially of the elements described herein further, and the invention described herein suitably may be practiced in the absence of any element which is not specifically disclosed herein.

We claim:

1. A method of reducing medication error and enhancing therapeutic compliance of an individual suffering from chronic obstructive pulmonary disease, said method comprising the steps of:

- (a) administering to the individual at least one single dispensing container wherein the container is prefilled with about 3 ml of a sterile, benzalkonium chloride-free, premixed, premeasured aqueous inhalation solution comprising a unit dose of a therapeutically effective amount of albuterol and ipratropium bromide; wherein the amount of albuterol is about 2.5 mg and the amount of ipratropium bromide is about 0.5 mg; the inhalation solution in the container is suitable for nebulization in a nebulizer; the inhalation solution in the container is stable, in that the inhalation solution is therapeutically effective following storage for 12 months at 25° C.; and
- (b) providing prescribing information; said prescribing information comprising dosage, administration, contraindication and adverse reaction information pertaining to the inhalation solution in the container;
- (c) wherein the contraindication information comprises information indicating that the inhalation solution in the container is contraindicated for humans with hypersensitivity to atropine and derivatives thereof; and
- (d) wherein the adverse reaction information comprises information indicating that lung disease, bronchitis, diarrhea, and pharyngitis may occur after administering the inhalation solution in the container.

2. The method of claim 1, wherein the prescribing information comprises information indicating that immediate hypersensitivity reactions to the inhalation solution in container may occur after administration of the inhalation solution, said hypersensitivity reaction including urticaria, angioedema, rash, pruritis, oropharyngeal edema, bronchospasm, and anaphylaxis; wherein the adverse reaction information comprises information indicating that precipitation or worsening of narrow-angle glaucoma, acute eye pain, blurred vision, paradoxical bronchospasm, pneumonia dyspepsia, urinary tract infection, wheezing, exacerbation of chronic obstructive pulmonary, disease symptoms, drowsiness, aching, flushing, upper respiratory tract infection, palpitations, taste perversion, elevated heart rate, sinusitis, back pain, sore throat and constipation may occur after administering the inhalation solution in the container.

3. A method of reducing medication error and enhancing therapeutic compliance of an individual suffering from chronic obstructive pulmonary disease, said method comprising the steps of:

- (a) administering to the individual at least one single dispensing container wherein the container is prefilled with about 3 ml of a sterile, premixed, premeasured aqueous inhalation solution free of benzalkonium chloride; the inhalation solution comprising water, edetate disodium, sodium chloride, and an acid to adjust the pH of the inhalation solution between about 3 and 4, and a unit dose of a therapeutically effective amount of albuterol and ipratropium bromide, wherein the amount of albuterol is about 2.50 mg/3 ml and the amount of ipratropium bromide is about 0.5 mg/3 ml; the inhalation solution in the container is suitable for nebulization in a nebulizer; the inhalation solution in the container is stable, in that the inhalation solution is therapeutically effective following storage for 12 months at 25° C.;
- (b) providing prescribing information; said prescribing information comprising efficacy, dosage and administration, contraindication and adverse reaction information pertaining to the inhalation solution in the container;
- (c) wherein the dosage and administration information indicates that the recommended dose of the inhalation solution is one container prefilled with 3 ml of the inhalation solution administered 4 times per day by nebulization with up to 2 additional doses allowed per day, if needed;
- (d) wherein the contraindication information comprises information indicating that the inhalation solution in the container is contraindicated for humans with hypersensitivity to atropine and derivatives thereof;
- (e) wherein the adverse reaction information comprises information indicating that immediate hypersensitivity reactions to the inhalation solution in the container may occur after administering the inhalation solution in the container, said hypersensitivity reaction including urticaria, angioedema, rash, pruritis, oropharyngeal edema, bronchospasm, and anaphylaxis;
- (f) wherein the adverse reaction information comprises information indicating that precipitation or worsening of narrow-angle glaucoma, acute eye pain, blurred vision, paradoxical bronchospasm, wheezing, exacerbation of chronic obstructive pulmonary disease symptoms, drowsiness, aching, flushing, upper respiratory tract infection, palpitations, taste perversion, elevated heart rate, sinusitis, back pain and sore throat may occur after administering the inhalation solution in the container; and
- (g) wherein the adverse reaction information comprises information indicating that, after administration of the inhalation solution in the container, one or more adverse reactions may occur; such adverse events comprising chest pain, diarrhea, dyspepsia, nausea, leg cramps, bronchitis, lung disease, pharyngitis, pneumonia, and urinary tract infection.

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