CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-503/S004

APPROVAL LETTER

NDA 20-503/S-004

3M Pharmaceuticals
3M Center, Building 260-6A-22
St. Paul, Minnesota 55144-1000

Attention: Marlene Peterson
Sr. Regulatory Coordinator

Dear Ms. Peterson:

Please refer to your supplemental new drug application dated September 22, 1997, received September 26, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Proventil HFA (albuterol sulfate) Inhalation Aerosol.

We acknowledge receipt of your submission dated March 31, 1998. The user fee goal date for this application is September 26, 1998.

This supplemental new drug application provides for the use of Proventil HFA for the prevention of exercise-induced bronchospasm in patients 12 years of age and older.

We have completed the review of this supplemental application, as amended, including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed marked-up draft labeling. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed marked-up labeling (text for the package insert, text for the patient package insert).

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-503/S-004." Approval of the submission by FDA is not required before the labeling is used.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Ms. Parinda Jani, Project Manager, at (301) 827-1064.

Sincerely yours,

John K. Jenkins, M.D., F.C.C.P.
Director
Division of Pulmonary Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-503/S004

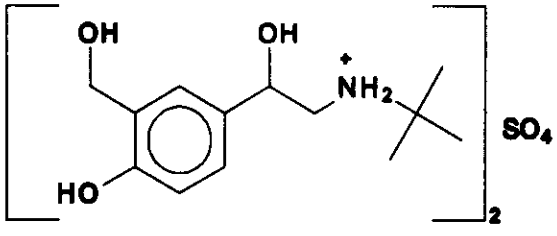
FINAL PRINTED LABELING

PROVENTIL® HFA
(~~A~~albuterol ~~S~~sulfate) Inhalation Aerosol~~)~~

FOR ORAL INHALATION ONLY

Prescribing Information

DESCRIPTION The active component of PROVENTIL HFA (~~A~~albuterol ~~S~~sulfate) Inhalation Aerosol~~)~~ is albuterol sulfate, USP racemic ~~α~~α[1][(*tert*-Butylamino)methyl]-4-hydroxy-m-xylene-α, α'-diol sulfate (2:1) (salt), a relatively selective beta$_2$-adrenergic bronchodilator having the following chemical structure:



Albuterol sulfate is the official generic name in the United States. The World Health Organization recommended name for the drug is salbutamol sulfate. The molecular weight of albuterol sulfate is 576.7, and the empirical formula is $(C_{13}H_{21}NO_3)_2 \bullet H_2SO_4$. Albuterol sulfate is a white to off-white crystalline solid. It is soluble in water and slightly soluble in ethanol. PROVENTIL HFA (~~A~~albuterol Sulfate) Inhalation Aerosol~~)~~ is a pressurized metered-dose aerosol unit for oral inhalation. It contains a microcrystalline suspension of albuterol sulfate in propellant HFA-134a (1,1,1,2-tetrafluoroethane), ethanol, and oleic acid.

Each actuation delivers 120 mcg albuterol sulfate, USP from the valve and 108 mcg albuterol sulfate, USP from the mouthpiece (equivalent to 90 mcg of albuterol base from the mouthpiece). Each canister provides 200 inhalations. It is recommended to prime the inhaler before using for the first time and in cases where the inhaler has not been used for more than 2 weeks by releasing four "test sprays" into the air, away from the face.

This product does not contain chlorofluorocarbons (CFCs) as the propellant.

CLINICAL PHARMACOLOGY

Mechanism of Action *In vitro* studies and *in vivo* pharmacologic studies have demonstrated that albuterol has a preferential effect on beta$_2$-adrenergic receptors compared with isoproterenol. While it is recognized that beta$_2$-adrenergic receptors are

the predominant receptors on bronchial smooth muscle, ~~recent~~ data indicate that there is a population of beta$_2$ receptors in the human heart ~~which comprise~~ existing in a concentration between 10% and 50% ~~of cardiac beta-adrenergic receptors~~. The precise function of these receptors ~~, however, is~~ has not ~~yet~~been established. (See **WARNINGS** for **Cardiovascular Effects.)**

Activation of beta$_2$-adrenergic receptors on airway smooth muscle leads to the activation of adenylcyclase and to an increase in the intracellular concentration of cyclic-3',5'-adenosine monophosphate (cyclic AMP). This increase of cyclic AMP leads to the activation of protein kinase A, which inhibits the phosphorylation of myosin and lowers intracellular ionic calcium concentrations, resulting in relaxation. Albuterol relaxes the smooth muscles of all airways, from the trachea to the terminal bronchioles. Albuterol acts as a functional antagonist to relax the airway irrespective of the spasmogen involved, thus protecting against all bronchoconstrictor challenges. Increased cyclic AMP concentrations are also associated with the inhibition of release of mediators from mast cells in the airway.

Albuterol has been shown in most clinical trials to have more effect on the respiratory tract, in the form of bronchial smooth muscle relaxation, ~~effect~~ than isoproterenol at comparable doses while producing fewer cardiovascular effects. Controlled clinical studies and other clinical experience have shown that inhaled albuterol, like other ~~However, all~~ beta-adrenergic agonist drugs, ~~including albuterol sulfate,~~ can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, symptoms, and/or electrocadiographic changes.

Preclinical Intravenous ~~albuterol~~ studies in rats with albuterol sulfate have demonstrated that albuterol crosses the blood-brain barrier and reaches brain concentrations amounting to ~~about~~approximately 5% of the plasma concentrations. In structures outside the blood-brain barrier (pineal and pituitary glands), ~~the drug achieves~~albuterol concentrations were found to be ~~of more than~~ 100 times those in the whole brain.

~~Studies in pregnant rats with tritiated albuterol have demonstrated that approximately 10% of the circulating maternal drug is transferred to the fetus. Disposition in fetal lungs is comparable to maternal lungs, but fetal liver disposition is 1% of maternal liver levels.~~ Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when β-agonists and methylxanthines were administered concurrently. The clinical significance of these findings ~~when applied to humans~~ is unknown.

Propellant HFA-134a is devoid of pharmacological activity except at very high doses in animals (380-1300 times the maximum human exposure based on comparisons of AUC values), primarily producing ataxia, tremors, dyspnea, or salivation. These are similar to effects produced by the structurally related chlorofluorocarbons (CFCs), which have been used extensively in metered dose inhalers.

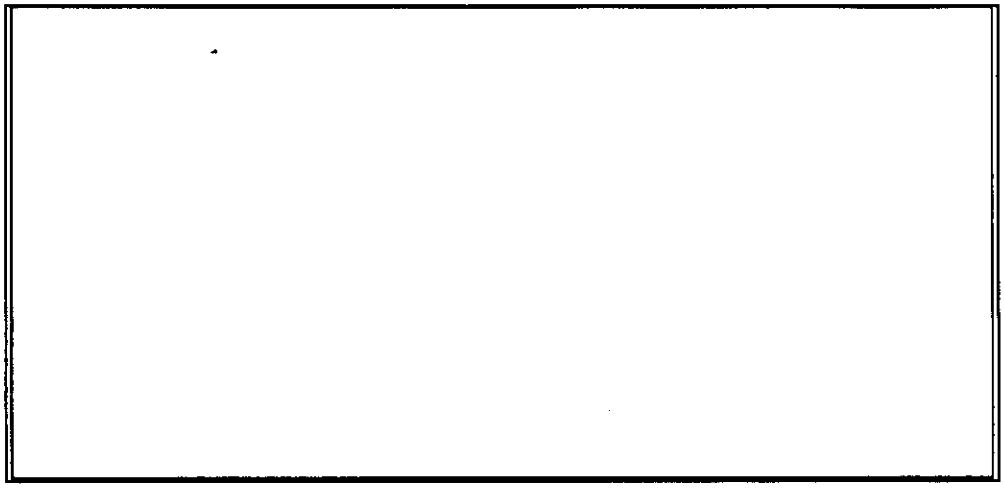
In animals and humans, propellant HFA-134a was found to be rapidly absorbed and rapidly eliminated, with an elimination half-life of 3-27 minutes in animals and 5-7 minutes in humans. Time to maximum plasma concentration (T_{max}) and mean residence time are both extremely short leading to a transient appearance of HFA-134a in the blood with no evidence of accumulation.

Pharmacokinetics In a single-dose bioavailablity study which enrolled 6 healthy, male volunteers, transient low albuterol levels (close the lower limit of quantitation) were ~~obtained~~ observed after administration of two puffs from both PROVENTIL HFA (~~A~~albuterol ~~S~~sulfate) Inhalation Aerosol~~)~~ and a CFC 11/12 propelled albuterol inhaler. No formal pharmacokinetic analyses were possible for either treatment, but systemic albuterol levels appeared similar.

Clinical Trials In a 12-week, randomized, double-blind, double-dummy, active- and placebo-controlled trial, 565 patients with asthma were evaluated for the bronchodilator efficacy of PROVENTIL HFA (~~A~~albuterol ~~S~~sulfate) Inhalation Aerosol~~)~~ (193 patients) in comparison to a CFC 11/12 propelled albuterol inhaler (186 patients) and an HFA-134a placebo inhaler (186 patients).

Serial FEV_1 measurements (shown below as percent change from test-day baseline) demonstrated that two inhalations of PROVENTIL HFA (~~A~~albuterol ~~S~~sulfate) Inhalation Aerosol~~)~~ produced significantly greater improvement in pulmonary function than placebo and produced outcomes which were clinically comparable to a CFC 11/12 propelled albuterol inhaler.

The mean time to onset of a 15 percent increase in FEV_1 was 6 minutes and the mean time to peak effect was 50 to 55 minutes. The mean duration of effect as measured by a 15 percent increase in FEV_1 was 3 hours. In some patients, duration of effect was as long as 6 hours.



In another clinical study in adults, two inhalations of Proventil HFA (~~A~~albuterol ~~S~~sulfate) Inhalation Aerosol~~)~~ taken 30 minutes before exercise prevented exercise-induced bronchospasm as demonstrated by the maintenance of FEV_1 within 80% of baseline values in the majority of patients.

INDICATIONS AND USAGE PROVENTIL HFA (~~A~~albuterol ~~S~~sulfate) Inhalation Aerosol~~)~~ is indicated in ~~patients~~adults and children 12 years of age and older for the treatment or prevention of bronchospasm with reversible obstructive airway disease and for the prevention of exercise-induced bronchospasm.

CONTRAINDICATIONS PROVENTIL HFA (~~A~~albuterol ~~S~~sulfate) Inhalation Aerosol~~)~~ is contraindicated in patients with a history of hypersensitivity to albuterol or any ~~of its~~ other Proventil HFA components.

WARNINGS

1. Paradoxical Bronchospasm: Inhaled albuterol sulfate can produce paradoxical bronchospasm that may be life threatening. If paradoxical bronchospasm occurs, PROVENTIL HFA (~~A~~albuterol ~~S~~sulfate) Inhalation Aerosol~~)~~ should be discontinued immediately and alternative therapy instituted. It should be recognized that paradoxical bronchospasm, when associated with inhaled formulations, frequently occurs with the first use of a new canister.

2. Deterioration of Asthma: Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient needs more doses of PROVENTIL HFA (~~A~~albuterol ~~S~~sulfate) Inhalation Aerosol~~)~~ than usual, this may be a marker of destabilization of asthma and requires re-evaluation of the patient and treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment, eg, corticosteroids.

3. Use of Anti-Inflammatory Agents: The use of beta-adrenergic-agonist bronchodilators alone may not be adequate to control asthma in many patients. Early consideration should be given to adding anti-inflammatory agents, eg, corticosteroids, to the therapeutic regimen.

4. Cardiovascular Effects: PROVENTIL HFA (~~A~~albuterol ~~S~~sulfate) Inhalation Aerosol~~)~~, like other beta-adrenergic agonists, can produce clinically significant cardiovascular effects in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of PROVENTIL HFA (~~A~~albuterol ~~S~~sulfate) Inhalation Aerosol~~)~~ at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Therefore, PROVENTIL HFA (~~A~~albuterol ~~S~~sulfate) Inhalation Aerosol~~)~~, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

5. Do Not Exceed Recommended Dose: Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma. The exact cause of death is unknown, but cardiac arrest following an unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is suspected.

6. Immediate Hypersensitivity Reactions: Immediate hypersensitivity reactions may occur after administration of albuterol sulfate, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, anaphylaxis, and oropharyngeal edema.

PRECAUTIONS

General Albuterol sulfate, as with all ~~Preparations containing~~ sympathomimetic amines ~~such as albuterol sulfate~~ should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive disorders, hyperthyrodism, or diabetes mellitus; and in patients who are unusually responsive to sympathomimetic amines. ~~who are unusually responsive to such agents and in patients with convulsive disorders, hyperthyroidism, or diabetes.~~ Clinically significant changes in systolic and diastolic blood pressure have been seen in individual patients and could be expected to occur in some patients after use of any beta-adrenergic bronchodilator.

~~**Hypokalemia:**~~ Large doses of intravenous albuterol have been reported to aggravate preexisting diabetes mellitus and ketoacidosis. As with other ~~B~~beta-~~adrenergic~~-agonists, ~~medications~~albuterol may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease is usually transient, not requiring supplementation.

Information for Patients See illustrated Patient's Instructions for Use. SHAKE WELL BEFORE USING. Patients should be given the following information:

KEEPING THE PLASTIC MOUTHPIECE CLEAN IS VERY IMPORTANT TO PREVENT MEDICATION BUILD-UP AND BLOCKAGE. THE MOUTHPIECE SHOULD BE WASHED, SHAKEN TO REMOVE EXCESS WATER AND AIR DRIED THOROUGHLY AT LEAST ONCE A WEEK. INHALER MAY CEASE TO DELIVER MEDICATION IF NOT PROPERLY CLEANED.

The mouthpiece should be cleaned (with the canister removed) by running warm water through the top and bottom for 30 seconds at least once a week. The mouthpiece must be shaken to remove excess water, then air dried thoroughly (such as overnight). Blockage from medication build-up or improper medication delivery may result from failure to thoroughly air dry the mouthpiece.

If the mouthpiece should become blocked (little or no medication coming out of the mouthpiece), the blockage may be removed by washing as described above.

If it is necessary to use the inhaler before it is completely dry, shake off excess water, replace canister, test spray twice away from face, and take the prescribed dose. After such use, the mouthpiece should be rewashed and allowed to air dry thoroughly.

The action of PROVENTIL HFA (~~A~~albuterol Sulfate) Inhalation Aerosol~~)~~ should last up to 4 to 6 hours. PROVENTIL HFA (~~A~~albuterol ~~S~~sulfate) Inhalation Aerosol~~)~~ should not be used more frequently than recommended. Do not increase the ~~number of puffs~~ dose or frequency of doses of PROVENTIL HFA (~~A~~albuterol ~~S~~sulfate) Inhalation Aerosol~~)~~ without consulting your physician. If you find that treatment with PROVENTIL HFA (~~A~~albuterol ~~S~~sulfate) Inhalation Aerosol~~)~~ becomes less effective for symptomatic relief, your symptoms become worse, and/or you need to use the product more frequently than usual, medical attention should be sought immediately. While you are taking PROVENTIL HFA (~~A~~albuterol ~~S~~sulfate) Inhalation Aerosol~~)~~, other inhaled drugs and asthma medications should be taken only as directed by your physician.

Common adverse effects of treatment with inhaled albuterol include palpitations, chest pain, rapid heart rate, tremor, or nervousness. If you are pregnant or nursing, contact your physician about use of PROVENTIL HFA (~~A~~albuterol ~~S~~sulfate) Inhalation Aerosol~~)~~. Effective and safe use of PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol) includes an understanding of the way that it should be administered. Use PROVENTIL HFA (~~A~~albuterol ~~S~~sulfate) Inhalation Aerosol~~)~~ only with the actuator supplied with the product. Discard the canister after 200 sprays have been used. (See Patient's Instructions for Use.)

Drug Interactions

1. Beta Blockers: Beta-adrenergic-receptor blocking agents not only block the pulmonary effect of beta agonists, such as PROVENTIL HFA (~~A~~albuterol ~~S~~sulfate) Inhalation Aerosol~~)~~, but may produce severe bronchospasm in asthmatic patients. Therefore, patients with asthma should not normally be treated with beta blockers. However, under certain circumstances, eg, as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-adrenergic-blocking agents in patients with asthma. In this setting, cardioselective beta blockers ~~could~~ should be considered, although they should be administered with caution.

2. Diuretics: The ECG changes and/or hypokalemia which may result from the administration of nonpotassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta agonists, especially when the recommended dose of the beta agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of beta-agonists with nonpotassium sparing diuretics.

3. Albuterol-Digoxin: Mean decreases of 16% and 22% in serum digoxin levels were demonstrated after single-dose intravenous and oral administration of albuterol, respectively, to normal volunteers who had received digoxin for 10 days. The clinical significance of these findings for patients with obstructive airway disease who are receiving albuterol and digoxin on a chronic basis is unclear; nevertheless, it would be prudent to carefully evaluate the serum digoxin levels in patients who are currently receiving digoxin and albuterol.

4. Monoamine Oxidase Inhibitors or Tricyclic Antidepressants: PROVENTIL HFA (~~A~~albuterol ~~S~~sulfate) Inhalation Aerosol~~)~~ should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of albuterol on the cardiovascular system may be potentiated.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

In a 2-year study in Sprague-Dawley rats, albuterol sulfate caused a ~~significant~~ dose-related increase in the incidence of benign leiomyomas of the mesovarium at ~~oral~~ and above dietary doses of ~~2, 10, and 50~~ mg/kg~~/day~~ (approximately ~~12, 60, and 300~~ 10 times the maximum recommended ~~human~~ daily inhalation dose for adults on a mg/m^2 basis). In another study this effect was blocked by the coadministration of propranolol, a non-selective beta-adrenergic antagonist. ~~The relevance of these findings to humans is not known.~~ In ~~A~~an 18-Month study in CD-1 mice albuterol sulfate showed no evidence of tumorigenicity at dietary doses of up to 500 mg/kg~~/day~~ (approximately ~~1560~~1700 times the maximum recommended ~~human~~ daily inhalation dose for adults on a mg/m^2 basis) ~~revealed no evidence of tumorigenicity~~. In a 22-month study in the Golden Hamster albuterol sulfate showed no evidence of tumorigenicity at dietary doses of up to 50

mg/kg (approximately 230 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis).

Albuterol sulfate was not mutagenic in the Ames test with or without metabolic activation using tester strains *S. typhimurium* TA1537, TA1538, and TA98 or *E. coli* WP2, WP2uvrA, and WP67. No forward mutation was seen in yeast strain *S. cerevisiae* S9 nor any mitotic gene conversion in yeast strain *S. cerevisiae* JD1 with or without metabolic activation. Fluctuation assays in *S. typhimurium* TA98 and *E. coli* WP2, both with metabolic activation, were negative. Albuterol sulfate was not clastogenic in a human peripheral lymphocyte assay or in an AH1 strain mouse micronucleus assay at intraperitoneal doses of up to 200 mg/kg.

Reproduction ~~S~~studies in rats demonstrated ~~with albuterol revealed~~ no evidence of ~~mutagenecis or~~ impaired fertility ~~in rats~~ at oral doses up to 50 mg/kg (approximately ~~300~~340 times the maximum recommended ~~human~~ daily inhalation dose for adults on a mg/m^2 basis).

Teratogenic Effects - Pregnancy Category C

Albuterol sulfate has been shown to be teratogenic in mice. A ~~reproduction~~ study in CD-1 mice ~~given albuterol sulfate~~ at a subcutaneously (sc) dose of ~~(0.025,~~ 0.25, ~~and 2.5~~ mg/kg) (less than the maximum recommended daily inhalation dose for adults on a mg/m^2 basis) showed cleft palate formation in 5 of 111 (4.5%) fetuses, ~~at 0.25 mg/kg~~ A sc dose of 2.5 mg/kg (approximately ~~equal to~~8 times the maximum recommended ~~human~~ daily inhalation dose for adults on a mg/m^2 basis) ~~and~~induced cleft palate formation in 10 of 108 (9.3%) fetuses, ~~at 2.5 mg/kg (approximately 10 times the maximum recommended human daily inhalation dose on a mg/m^2 basis~~). The drug did not induce cleft palate formation at the low dose. ~~None was observed at~~ 0.025 mg/kg ~~(approximately one tenth~~ (less than the maximum recommended daily inhalation dose for adults on a mg/m^2 basis). Cleft palate also occurred in 22 of 72 (30.5%) fetuses from females treated with 2.5 mg/kg isoproterenol (positive control) administered subcutaneously (approximately 8 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis). A reproduction study ~~with oral albuterol~~ in Stride Dutch rabbits revealed cranioschisis in 7 of 19 (37%) fetuses when albuterol sulfate was administered orally at 50 mg/kg dose (approximately ~~600~~680 times the maximum recommended ~~human~~ daily inhalation dose for adults on a mg/m^2 basis).

Studies in pregnant rats with tritiated albuterol have demonstrated that approximately 10% of the circulating maternal drug is transferred to the fetus. Disposition in fetal lungs is comparable to maternal lungs, but fetal liver disposition is 1% of maternal liver levels.

In ~~a separate~~ an inhalation reproduction study in Sprague-Dawley rats, ~~using~~ the albuterol sulfate/HFA-134a formulation, ~~albuterol sulfate~~ did not exhibit any teratogenic effects at 10.5 mg/kg~~/day~~ (approximately ~~65~~70 times the maximum recommended

~~human~~ daily inhalation dose for adults on a mg/m^2 basis).

There are~~, however,~~ no adequate and well-controlled studies of PROVENTIL HFA (~~A~~albuterol ~~S~~sulfate) Inhalation Aerosol~~)~~ or albuterol sulfate in pregnant women. Because animal reproduction studies are not always predictive of human response, PROVENTIL HFA (~~A~~albuterol ~~S~~sulfate) Inhalation Aerosol~~)~~ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Various congenital anomalies, including cleft palate and limb defects, have been reported in the offspring of patients being treated with albuterol. Some of the mothers were taking multiple medications during their pregnancies. Because no consistent pattern of defects can be discerned, a relationship between albuterol use and congenital anomalies cannot be established.

Use in Labor and Delivery
Because of the potential for beta-agonist interference with uterine contractility, use of PROVENTIL HFA (~~A~~albuterol ~~S~~sulfate) Inhalation Aerosol~~)~~ for relief of bronchospasm during labor should be restricted to those patients in whom the benefits clearly outweigh the risk.

Tocolysis: Albuterol has not been approved for the management of pre-term labor. The benefit:risk ratio when albuterol is administered for tocolysis has not been established. Serious adverse reactions, including pulmonary edema, have been reported during or following treatment of premature labor with beta$_2$-agonists, including albuterol.

Nursing Mothers
Plasma levels of albuterol sulfate and HFA-134a after inhaled therapeutic doses are very low in humans, but it is not known whether the components~~ecomponents~~ of PROVENTIL HFA (~~A~~albuterol ~~S~~sulfate) Inhalation Aerosol~~)~~ are excreted in human milk.

Because of the potential for tumorigenicity shown for albuterol in animal studies and lack of experience with the use of PROVENTIL HFA (~~A~~albuterol ~~S~~sulfate) Inhalation Aerosol~~)~~ by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Caution should ~~be~~ exercised when albuterol sulfate is administered to a nursing woman.

Pediatrics
The safety and effectiveness of PROVENTIL HFA (~~A~~albuterol ~~S~~sulfate) Inhalation Aerosol~~)~~ in pediatric patients below the age of 12 years have not been established.

Geriatrics

PROVENTIL HFA (~~A~~albuterol ~~S~~sulfate) Inhalation Aerosol~~)~~ has not been studied in a geriatric population. As with other $beta_2$-agonists, special caution should be observed when using PROVENTIL HFA (~~A~~albuterol ~~S~~sulfate) Inhalation Aerosol~~)~~ in elderly patients who have concomitant cardiovascular disease that could be adversely affected by this class of drug.

ADVERSE REACTIONS Adverse reaction information concerning PROVENTIL HFA (~~A~~albuterol ~~S~~sulfate) Inhalation Aerosol~~)~~ is derived from a 12-week, double-blind, double-dummy study which compared PROVENTIL HFA (~~A~~albuterol ~~S~~sulfate) Inhalation Aerosol~~)~~, a CFC 11/12 propelled albuterol inhaler, and an HFA-134a placebo inhaler in 565 asthmatic patients. The following table lists the incidence of all adverse events (whether considered by the investigator drug related or unrelated to drug) from this study which occurred at a rate of 3% or greater in the PROVENTIL HFA (~~A~~albuterol ~~S~~sulfate) Inhalation Aerosol~~)~~ treatment group and more frequently in the PROVENTIL HFA (~~A~~albuterol ~~S~~sulfate) Inhalation Aerosol~~)~~ treatment group than in the placebo group. Overall, the incidence and nature of the adverse reactions reported for PROVENTIL HFA (~~A~~albuterol ~~S~~sulfate) Inhalation Aerosol~~)~~ and a CFC 11/12 propelled albuterol inhaler were comparable.

Adverse Experience Incidences (% of patients) In a Large 12-week Clinical Trial*

Body System/ Adverse Event (Preferred Term)		Proventil HFA (~~A~~albuterol ~~S~~sulfate) Inhalation Aerosol~~)~~ (N = 193)	CFC 11/12 Propelled Albuterol Inhaler (N = 186)	HFA-134a Placebo Inhaler (N = 186)
Application Site Disorders	Inhalation Site Sensation	6	9	2
	Inhalation Taste Sensation	4	3	3
Body as a Whole	Allergic Reaction/Symptom	6	4	<1
	Back Pain	4	2	3
	Fever	6	2	5
Central and Peripheral Nervous System	Tremor	7	8	2
Gastrointestinal System	Nausea	10	9	5
	Vomiting	7	2	3
Heart Rate and Rhythm Disorder	Tachycardia	7	2	<1
Psychiatric Disorders	Nervousness	7	9	3
Respiratory System Disorders	Respiratory Disorder (unspecified)	6	4	5
	Rhinitis	16	22	14
	Upper Resp Tract Infection	21	20	18
Urinary System Disorder	Urinary Tract Infection	3	4	2

*This table includes all adverse events (whether considered by the investigator drug related or unrelated to drug) which occurred at an incidence rate of at least 3.0% in the PROVENTIL HFA (~~A~~albuterol ~~S~~sulfate~~)~~ Inhalation Aerosol~~)~~ group and more frequently in the PROVENTIL HFA (~~A~~albuterol ~~S~~sulfate~~)~~ Inhalation Aerosol~~)~~ group than in the HFA-134a placebo inhaler group.

Adverse events reported by less than 3% of the patients receiving PROVENTIL HFA (~~A~~albuterol ~~S~~sulfate) Inhalation Aerosol~~)~~, and by a greater proportion of PROVENTIL HFA (~~A~~albuterol ~~S~~sulfate) Inhalation Aerosol~~)~~ patients than placebo patients, which have the potential to be related to PROVENTIL HFA (~~A~~albuterol ~~S~~sulfate) Inhalation Aerosol~~)~~ include: dysphonia, increased sweating, dry mouth, chest pain, edema, rigors, ataxia, leg cramps, hyperkinesia, eructation, flatulence, tinnitus, diabetes mellitus, anxiety, depression, somnolence, rash. Palpitation and dizziness have also been observed with PROVENTIL HFA.
In small, cumulative dose studies, tremor, nervousness, and headache appeared to be dose related.

Rare cases of urticaria, angioedema, rash, bronchospasm, and oropharyngeal edema have been reported after the use of inhaled albuterol. In addition, albuterol, like other sympathomimetic agents, can cause adverse reactions such as hypertension, angina, vertigo, central nervous system stimulation, insomnia, headache, and drying or irritation of the oropharynx.

OVERDOSAGE The expected symptoms with overdosage are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the symptoms listed under ADVERSE REACTIONS, eg, seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats per minute, arrhythmias, nervousness, headache, tremor, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and insomnia. Hypokalemia may also occur. As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of PROVENTIL HFA (~~A~~albuterol ~~S~~sulfate) Inhalation Aerosol~~)~~. Treatment consists of discontinuation of PROVENTIL HFA (albuterol sulfate) Inhalation Aerosol together with appropriate symptomatic therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of PROVENTIL HFA (albuterol sulfate) Inhalation Aerosol.

The oral median lethal dose of albuterol sulfate in mice ~~and rats was~~is greater than 2,000 mg/kg (approximately ~~6,000 and 12,000~~ 6,800 times the maximum recommended ~~human~~ daily inhalation dose~~, respectively,~~ for adults on a mg/m^2 basis). In mature rats, the subcutaneous median lethal dose of albuterol sulfate is approximately 450 mg/kg (approximately 3000 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis). In small young rats, the subcutaneous median lethal dose is approximately 2000 mg/kg (approximately 14,000 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis).The inhalation median lethal dose ~~could~~has not been determined in animals.

~~Treatment consists of discontinuation of PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol) together with appropriate symptomatic therapy. The judicious use of a~~

~~cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol).~~

DOSAGE AND ADMINISTRATION For treatment of acute episodes of bronchospasm or prevention of asthmatic symptoms, the usual dosage for adults and children 12 years of age and older is 2 inhalations repeated every 4 to 6 hours. More frequent administration or a larger number of inhalations is not recommended. In some patients, 1 inhalation every 4 hours may be sufficient. Each actuation of PROVENTIL HFA (Aalbuterol Ssulfate) Inhalation Aerosol) delivers 108 mcg of albuterol sulfate (equivalent to 90 mcg of albuterol base) from the mouthpiece. It is recommended to prime the inhaler before using for the first time and in cases where the inhaler has not been used for more than 2 weeks by releasing four "test sprays" into the air, away from the face.

Exercise Induced Bronchospasm Prevention: The usual dosage for adults and children 12 years of age and older is 2 inhalations 30 minutes before exercise.

To maintain proper use of this product it is important that the mouthpiece be washed and dried thoroughly at least once a week. The inhaler may cease to deliver medication if not properly cleaned and dried thoroughly. See **Information for Patients**. Keeping the plastic mouthpiece clean is very important to prevent medication build-up and blockage. The inhaler may cease to deliver medication if not properly cleaned and air dried thoroughly. If the mouthpiece becomes blocked, washing the mouthpiece will remove the blockage.

If a previously effective dosage regimen fails to provide the usual response, this may be a marker of destabilization of asthma and requires reevaluation of the patient and the treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment, e.g., corticosteroids.

HOW SUPPLIED PROVENTIL HFA (Aalbuterol Ssulfate) Inhalation Aerosol) is supplied as a pressurized aluminum canister with a yellow plastic actuator and orange dust cap each in boxes of one. Each actuation delivers 120 mcg of albuterol sulfate from the valve and 108 mcg of albuterol sulfate from the mouthpiece (equivalent to 90 mcg of albuterol base). Canisters with a labeled net weight of 6.7 g contain 200 inhalations (NDC 0085-1132-01).

CAUTION Federal law prohibits dispensing without prescription. Store between 15°C and 25°C (59°F and 77°F). For best results, canister should be at room temperature before use.

SHAKE WELL BEFORE USING

The yellow actuator supplied with PROVENTIL HFA (~~A~~albuterol ~~S~~sulfate) Inhalation Aerosol~~)~~ should not be used with any other product canisters, and ~~only~~

~~with the actuator provided. The~~ **actuator** from other products **should not be used with** ~~other aerosol medications~~ a Proventil-HFA canister. The correct amount of medication in each canister cannot be assured after 200 actuations, even though the canister is not completely empty. The canister should be discarded when the labeled number of actuations have been used.

Avoid spraying in eyes. Contents under pressure. Do not puncture or incinerate. Exposure to temperatures above 120^{0}F may cause bursting. Keep out of reach of children.

PROVENTIL HFA (~~A~~albuterol ~~S~~sulfate) Inhalation Aerosol~~)~~ does not contain chlorofluorocarbons (CFCs) as the propellant.

Developed and Manufactured
by
3M Health Care Limited
Loughborough, UK

or

3M Pharmaceuticals
Northridge, CA 91324

KEY® Key Pharmaceuticals, Inc.
Kenilworth, NJ 07033 USA

Rev. 8/97

Attention Pharmacist:
Detach "Patients's Instructions for Use"
from package insert and dispense with the product

PROVENTIL HFA
(~~A~~albuterol ~~S~~sulfate) Inhalation Aerosol~~)~~
Patient's Instructions For Use

Figure 1

Figure 2

Before using your PROVENTIL H FA (~~A~~albuterol ~~S~~sulfate) Inhalation Aerosol~~)~~, read complete instructions carefully.

Please note that:

✓

indicates that this inhalation aerosol does not contain chlorofluorocarbons (CFCs) as the propellant.

1. SHAKE THE INHALER WELL immediately before each use. **Then remove the cap from the mouthpiece** (see Figure 1). **Check mouthpiece for foreign objects prior to use.** Make sure the canister is fully inserted into the actuator.

2. As with all aerosol medications, it is recommended to prime the inhaler before using for the first time and in cases where the inhaler has not been used for more than 2 weeks. Prime by releasing four "test sprays" into the air, away from your face.

3. BREATHE OUT FULLY THROUGH THE MOUTH, expelling as much air from your lungs as possible. Place the mouthpiece fully into the mouth holding the inhaler in its upright position (see Figure 2) and closing the lips around it.

4. WHILE BREATHING IN DEEPLY AND SLOWLY THROUGH THE MOUTH, FULLY DEPRESS THE TOP OF THE METAL CANISTER with your index finger (see Figure 2).

5. HOLD YOUR BREATH AS LONG AS POSSIBLE, up to 10 seconds. Before breathing out, remove the inhaler from your mouth and release your finger from the canister.

6. If your physician has prescribed additional puffs, wait 1 minute, shake the inhaler again and repeat steps 2 through 4. Replace the cap after use.

7. KEEPING THE PLASTIC MOUTHPIECE CLEAN IS EXTREMELY IMPORTANT TO PREVENT MEDICATION BUILD-UP AND BLOCKAGE. THE MOUTHPIECE SHOULD BE WASHED, SHAKEN TO REMOVE EXCESS WATER AND AIR DRIED THOROUGHLY AT LEAST ONCE A WEEK. INHALER MAY STOP SPRAYING IF NOT PROPERLY CLEANED

Routine Cleaning instructions:
Step 1. To clean, remove the canister and mouthpiece cap. Wash the mouthpiece through the top and bottom with warm running water for 30 seconds at least once a week (See Figure A). **Never immerse the metal canister in water.**

Figure A
Wash mouthpiece under warm running water

Figure B
Allow mouthpiece to air dry, such as overnight

Figure C
When blocked little or no medicine comes out

Step 2. To dry, shake off excess water and let the mouthpiece air dry thoroughly, such as overnight (See Figure B). When the mouthpiece is dry, replace the canister and the mouthpiece cap. Blockage from medication build-up is more likely to occur if the mouthpiece is not allowed to air dry thoroughly.

IF YOUR INHALER HAS BECOME BLOCKED (little or no medication coming out of the mouthpiece, see Figure C), wash the mouthpiece as described in STEP 1 and air dry thoroughly as described in STEP 2.

IF YOU NEED TO USE YOUR INHALER BEFORE IT IS COMPLETELY DRY, SHAKE OFF EXCESS WATER, replace the canister, and test spray twice into the air, away from your face, to remove most of the water remaining in the mouthpiece. Then take your dose as prescribed. **After such use, rewash and air dry thoroughly as described in STEPS 1 and 2.**

~~7. As with all aerosol medications, it is recommended to test the inhaler before using for the first time and in cases where the inhaler has not been used for more than 2 weeks. Test by releasing four "test sprays" into the air, away from your face.~~

8. The correct amount of medication in each inhalation cannot be assured ~~PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol) will deliver at least~~ after 200 ~~sprays~~actuations even though the canister is not completely empty. The canister should be discarded when the labeled number of actuations have been used. ~~However, after 200 sprays, the amount of drug delivered per spray may not be consistent. You should keep track of the number of sprays used from each canister of PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol) and discard the canister after 200 sprays.~~ Before you reach the specific number of actuations, you should consult your physician to determine whether a refill is needed. Just as you should not take extra doses without consulting your physician, you also should not stop using Proventil HFA without consulting your physician.

You may notice a slightly different taste or spray force than you are used to with PROVENTIL HFA (~~A~~albuterol ~~S~~sulfate) Inhalation Aerosol~~)~~, compared to other albuterol inhalation aerosol products.

DOSAGE:
Use only as directed by your physician.

WARNINGS:
The action of PROVENTIL HFA (~~A~~albuterol ~~S~~sulfate) Inhalation Aerosol~~)~~ should last up to 4 to 6 hours. PROVENTIL HFA (~~A~~albuterol ~~S~~sulfate) Inhalation Aerosol~~)~~ should not be used more frequently than recommended. Do not increase the number of puffs or frequency of doses of PROVENTIL HFA (~~A~~albuterol ~~S~~sulfate) Inhalation Aerosol~~)~~ without consulting your physician. If you find that treatment with PROVENTIL HFA (~~A~~albuterol ~~S~~sulfate) Inhalation Aerosol~~)~~ becomes less effective for symptomatic relief, your symptoms become worse, and/or you need to use the product more frequently than usual, medical attention should be sought immediately. While you are taking PROVENTIL HFA (~~A~~albuterol ~~S~~sulfate) Inhalation Aerosol~~)~~, other inhaled drugs should be taken only as directed by your physician. If you are pregnant or nursing, contact your physician about the use of PROVENTIL HFA (~~A~~albuterol ~~S~~sulfate) Inhalation Aerosol~~)~~.

Common Adverse effects of treatment with PROVENTIL HFA (~~A~~albuterol ~~S~~sulfate)

Inhalation Aerosol) include palpitations, chest pain, rapid heart rate, tremor, or nervousness. Effective and save use of PROVENTIL HFA (Aalbuterol Ssulfate) Inhalation Aerosol) includes an understanding of the way that it should be administered. Use PROVENTIL HFA (Aalbuterol Ssulfate) Inhalation Aerosol) only with the yellow actuator supplied with the product. The PROVENTIL HFA actuator should not be used with other aerosol medications.

For best results use at room temperature. Avoid exposing product to extreme heat and cold.

Shake well before use.

Contents Under Pressure.
Do not puncture. Do not store near heat or open flame. Exposure to temperatures above 120°F may cause bursting. Never throw container into fire or incinerator. Store between 15°C and 25°C (59°F and 77°F). Avoid spraying in eyes. Keep out of reach of children.

Further Information: Your PROVENTIL HFA (Aalbuterol Ssulfate) Inhalation Aerosol) does not contain chlorofluorocarbons (CFCs) as the propellant. Instead the inhaler contains a hydrofluoroalkane (HFA-134a) as the propellant.

Developed and Manufactured
by
3M Health Care Limited
Loughborough, UK

or

3M Pharmaceuticals
Northridge, CA 91324

for

KEY• Key Pharmaceuticals, Inc.
Kenilworth, NJ 07033 USA

Rev. 8/97
U.S. Patent 5,225,183

cc:
Archival NDA 20-503
HFD-570/Div. Files
HFD-570/P.Jani
HFD-570/Johnson/9-14-98
HFD-570/Meyer/9-14-98
HFD-570/Schroeder/9-10-98
HFD-570/Poochikian
HFD-570/Whitehurst/9-10-98
HFD-570/Sheeversh/9-10-98
HFD-570/Schumaker/9-9-98
HFD-570/Guo/9-10-98
HFD-570/Wilson/9-14-98
HFD-570/Uppoor
HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-102/ADRA (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-95/DDMS (with labeling)
HFD-820/DNDC Division Director
DISTRICT OFFICE

Drafted by: pj/August 27, 1998
Initialed by:
final:pj/September 16, 1998
filename: c:\my documents\n20503ap.004

APPROVAL (AP)

Project Manager's Labeling Review

Project Manager: Parinda Jani Date: July 2, 1998
NDA: 20503/S-004
Product: Proventil HFA
Sponsor: 3M Pharmaceuticals
Submission Date: September 22, 1997

Supplement S-004, an efficacy supplement, provides for the treatment of exercise-induced bronchospasm in patients 12 years of age and older.

Background: Proventil HFA was approved August 15, 1996. The beta-agonists class labeling document was finalized September 1996. The following changes are recommended based on the final class labeling document and the Ventolin MDI labeling, which was approved November 12, 1997 (class labeling and additional changes recommended by the reviewers) to have consistent labeling for the albuterol products.

DESCRIPTION:

At the end of the first sentence add "having the following chemical structure."

CLINICAL PHARMACOLOGY:

Mechanism of Action: First paragraph - Revise the second sentence to "While it is recognized that $beta_2$-adrenergic receptors are the predominant receptors on bronchial smooth muscle, data indicate that there is a population of $beta_2$-receptors in the human heart existing in a concentration between 10% and 50%. The precise function of these receptors has not been established."

Third paragraph - Revise this paragraph to "Albuterol has been shown in most clinical trials to have more effect on the respiratory tract, in the form of bronchial smooth muscle relaxation, than isoproterenol at comparable doses while producing fewer cardiovascular effects. Controlled clinical studies and other clinical experience have shown that inhaled albuterol, like other beta-adrenergic agonists drugs, can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, symptoms, and/or electrocadiographic changes.

Note: The albuterol products labeling contains statements of isoproterenol comparison. Whether these statements should be included in the Proventil-HFA labeling or not, should be decided by the medical officer.

Preclinical: Delete "albuterol" replace it with "albuterol sulfate" and delete "about" and replace it with "approximately" in the first sentence. Delete "the drug achieves" replace it with "albuterol concentrations were found to be".

CONTRAINDICATIONS:

Add "albuterol or" after "hypersensitivity to".

WARNINGS:

Warning # 5, Do Not Exceed Recommended Dose, is not part of the class labeling document. Whether it needs to stay, or be deleted from the labeling, should be decided by the medical officer.

PRECAUTIONS: General - This section should be revised as recommended in the class labeling document as follows:

Albuterol sulfate, as with all sympathomimetic amines should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive disorders, hyperthyrodism, or diabetes mellitus; and in patients who are unusually responsive to sympathomimetic amines. Clinically significant changes in systolic and diastolic blood pressure have been seen in individual patients and could be expected to occur in some patients after use of any beta-adrenergic bronchodilator.

Large doses of intravenous albuterol have been reported to aggravate preexisting diabetes mellitus and ketoacidosis. As with other beta-agonists, albuterol may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease is usually transient, not requiring supplementation.

Information for Patients: Sixth paragraph - Delete "number of puffs" replace it with "dose".

Drug Interactions: Beta Blockers - Delete "could" replace it with "should" from the last sentence.

Carcinogenesis, Mutagenesis, and Impairment of Fertility and Teratogenic Effects - Pregnancy Category C sections should be revised to the latest Division's recommendations for the albuterol products. The corresponding human doses calculations should be verified by the pharmacologists.

The "Tocolysis" statement should be added to the PRECAUTIONS section.

OVERDOSAGE:

The medial lethal dose statement should be revised to the latest Division's recommendations for the albuterol products. The corresponding human doses calculations should be verified by the pharmacologists.

DOSAGE AND ADMINISTRATION:

The priming instructions should be added to this section. Also the statement "If a previously effective dosage regimen fails to provide the usual response, this may be a marker of destabilization of asthma and requires reevaluation of the patient and the treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment, e.g., corticosteroids." should be added to this section.

Also the statement "The yellow adapter supplied with PROVENTIL HFA (Albuterol Sulfate Inhalation Aerosol) should not be used with any other product canisters, and from other products should not be used with a Proventil-HFA canister. The correct amount of medication in each canister cannot be assured after 200 actuations, even though the canister is not completely empty. The canister should be discarded when the labeled number of actuations have been used." should be added.

PATIENT'S INSTRUCTION FOR USE LEAFLET:

Item # 8 should be revised to "The correct amount of medication in each inhalation cannot be assured after 200 actuations even though the canister is not completely empty. The canister should be discarded when the labeled number of actuations have been used. Before you reach the specific number of actuations, you should consult your physician to determine whether a refill is needed. Just as you should not take extra doses without consulting your physician, you also should not stop using Proventil HFA without consulting your physician. "

There are no changes recommended to the other sections of the package insert.

/S/

Parinda Jani
Project Manager

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-503/S004

MEDICAL REVIEW(S)

MEDICAL OFFICER REVIEW
Division of Pulmonary Drug Products (HFD-570)

APPLICATION #: NDA 20-503 **APPLICATION TYPE: NDA**

SPONSOR: 3M Pharmaceuticals **PRODUCT/PROPRIETARY NAME: Proventil HFA**

USAN / Established Name: Albuterol Sulfate Inhalation Aerosol

CATEGORY OF DRUG: Short Acting Beta-Agonist **ROUTE OF ADMINISTRATION: Oral Inhalation**

MEDICAL REVIEWER: Susan Johnson, Pharm.D. **REVIEW DATE: July 24, 1998**

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
September 22, 1997	September 26, 1997	Efficacy Supplement	EIB in Adults

Overview of Application/Review:
Ms. Jani, the Project Manager, has provided comments in her July 2, 1998 review regarding labeling changes to establish consistency of the Proventil HFA label with the division's beta-agonist class labeling and other current conventions. All of the changes proposed in Ms. Jani's review are acceptable on this basis and the following additional comments are provided:
1. CLINICAL PHARMACOLOGY, Mechanism of Action: Final two paragraphs of the VENTOLIN labeling, containing comparisons of albuterol and isoproterenol, need not be added to the PROVENTIL HFA labeling.
2.CONTRAINDICATIONS: Change "albuterol or any of its to "albuterol or any other PROVENTIL HFA components."
3.WARNING #5 may be retained by the sponsor on the basis of safety, although the issues addressed in the statement have been covered elsewhere in the class labeling.

Recommended Regulatory Action: N drive location:

New Clinical Studies: _____ Clinical Hold _____ Study May Proceed

NDAs:

Efficacy / Label Supp.: __X__ Approvable _____ Not Approvable

Signed: Medical Reviewer /S/ Date: 7/24/98

Medical Team Leader: _____ Date: _____

APPEARS THIS WAY
ON ORIGINAL

MEDICAL OFFICER REVIEW

Division of Pulmonary Drug Products (HFD-570)

APPLICATION #: 20-503 **APPLICATION TYPE: NDA**

SPONSOR: 3M Pharmaceuticals **PRODUCT/PROPRIETARY NAME: Proventil-HFA**

USAN / Established Name: Albuterol sulfate MDI

CATEGORY OF DRUG: Beta-agonist **ROUTE OF ADMINISTRATION: Oral Inhalation**

MEDICAL REVIEWER: Susan Johnson **REVIEW DATE: June 26, 1998**

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
September 22, 1997	September 26, 1997	Efficacy Supplement	Adult EIB

Overview of Application/Review:
This submission contains a study report of a four-way, single-dose crossover exercise challenge trial comparing Proventil HFA, Ventolin, Proventil (CFC) and HFA-134a placebo which supports claims for an indication in the prevention of exercise-induced bronchospasm in adults and children age 12 years and over.

Outstanding Issues:
The supplement is approvable pending communication of two minor issues to the sponsor and their adequate resolution. Ms. Jani, the project manager, will provide additional comments on the proposed labeling.

Recommended Regulatory Action: N drive location:

New Clinical Studies: _____ Clinical Hold _____ Study May Proceed

NDAs:

Efficacy / Label Supp.: ___X___ Approvable _____ Not Approvable

Signed: Medical Reviewer /S/ Date: 6-26-98

Medical Team Leader /S/ Date: 6/26/98

Team Leader: I concur w Dr. Johnson's findings / reviews. Particularly, I think the dosing recommendations should be as aligned to the current products as the data allow. /S/

Introduction

Trial 1150-SILV, entitled "Single-Dose Safety and Efficacy Study of HFA-134a Salbutamol Sulfate (Proventil-HFA), Ventolin, Proventil, and HFA-134a Placebo in Patients with Exercise Induced Asthma," has been submitted in support of an indication for Proventil-HFA in the prevention of exercise induced asthma in adults and children age 12 years and older. The proposed dose is two inhalations to be administered 30 minutes prior to exercise.

The first patient was enrolled June 26, 1995 and the final patient was completed October 19, 1995. One protocol amendment was made prior to initiation of the trial.

Protocol

This was a randomized, single-blind (evaluator-blind), placebo-controlled, four-period crossover study. Twenty patients between the ages of 12 and 50 who had a history of at least 12 months of mild to moderate asthma were eligible for enrollment into the trial if they used a short-acting inhaled beta agonist and exhibited a pre-study FEV_1 of at least 70 percent of predicted normal. Eligible patients exhibited exercise-induced bronchospasm with a decrease in FEV_1 of at least 20 percent, but not more than 50 percent, within 30 minutes following each of two prestudy exercise challenge tests. Patients were required to be non-smokers.

Patients were not enrolled if they had evidence of clinically significant concomitant disease. They were also excluded from the study if their asthma was unstable, as defined by a change in their asthma therapy or a visit to a hospital or emergency department for asthma during the four weeks prior to the study. Theophylline, salmeterol, oral beta-agonists, cromolyn sodium, nedocromil sodium, oral or injectable corticosteroids, monoamine oxidase inhibitors, tricyclic antidepressants and beta blockers were required to be washed out, then withheld for the duration of the study.

Following screening and pre-study tests, patients completed four study periods, separated by between 3 and 10 days. Study periods were initiated between 7 and 11 A.M. and within 2 hours of the same time of day as the prestudy period. Predose FEV_1 at each period was required to be within 10 percent of the prestudy FEV_1 and not less than 70 percent of predicted normal. Pulse rate, sitting blood pressure and a 12-lead ECG were also assessed prior to dosing, then patients received two puffs of the assigned medication under the supervision of the study coordinator. The pulmonary function technician, exercise-challenge assistant and investigator were blinded to identity of the study medication. The exercise challenge commenced 30 minutes after dosing. During the challenge, heart rate and rhythm were continuously monitored with an ECG. Blood pressure was assessed every 2 minutes. PFT's were assessed at 5, 10, 15, 30, 45, 60, 75 and 90 minutes after the exercise challenge. Adverse events were recorded throughout the study periods.

The exercise challenge at the prestudy clinic visit and at study Periods 1 to 4 consisted of exercise on a treadmill with speed and incline adjusted for patients' heart rates to

reach 80 to 90 percent of maximum predicted (target) heart rate after approximately 2 to 4 minutes of exercise. Maximum predicted heart rate was defined as 220 minus age in years. The target heart rate was maintained for at least six minutes using adjustments in the speed and incline of the treadmill, for a total exercise period of 8 to 10 minutes. The test was stopped and rescue albuterol was administered if a patient experienced a drop in FEV_1 of 50 percent or more.

Data from all randomized patients were included in an intent to treat analysis of safety and efficacy. The protocol-defined primary efficacy endpoint was the largest change from baseline FEV_1 following an exercise challenge (i.e., the largest positive or negative percent change over the 90 minute post-exercise period). The secondary efficacy endpoint described in the protocol was the comparison of the number of protected, partially protected and unprotected patients in each treatment group, based on largest percentage change in FEV_1. The single protocol amendment specified that the secondary analysis was not going to be conducted.

The study report details different analyses than the protocol. The primary endpoint was modified to be the smallest percent change from predose, although the study report does not describe when this decision was made. It does relate that the following secondary endpoints were adopted prior to unblinding the treatment codes: the smallest absolute change from predose FEV_1, the smallest change as a percent of predicted and a comparison of the smallest changes among patients who were and were not protected (patients were considered unprotected if they experienced a drop in FEV_1 of at least 20 percent).

Comment: The decision to use the smallest, rather than largest, percent change as a primary endpoint has merit in that the smallest percent change will capture the differences among treatments at the nadir of their effect. This will be discussed later in the review in terms of the study outcomes.

Additional analyses were planned and conducted after unblinding the data. These included mean percent change, mean absolute change and mean change from predose as a percent of predicted for FEV_1 at each of the eight times post-exercise.

Each change outcome was analyzed using an ANOVA with treatment, period, sequence and patient-within-sequence predictors in the model. The number of protected/unprotected patients in each active treatment group were compared to the number in the HFA-134a placebo group using McNemar's test. For each efficacy analysis, tests were two-sided and conducted at the $\alpha = .017 = (0.05/3)$ level of significance. Sample size was based on detecting a 10 percent difference in mean maximal decrease in FEV_1 (an unanalyzed outcome) between active and placebo with a power of at least 90 percent.

Comment: This trial was powered to detect differences between active and placebo treatments and the sensitivity of this trial to detect differences among the active treatments is unknown. Given this design and the relatively mild nature of asthma in

this patient population, sensitivity of the study to detect differences among the active treatments is limited and the statistical outcomes related to comparison of active treatments provide limited information about the true differences among them. Conclusions on the comparison of active treatments must be based largely on clinical, rather than statistical, interpretation of the outcomes.

Patient Disposition

Of the 33 patients screened, 20 were randomized and completed the trial. Thirteen patients failed to qualify and the reasons provided appear consistent with the protocol. There were seven females and 13 males who completed the trial, ranging in age from 14 to 43 years with a mean of 23.9 years. Sixteen patients were Caucasian. No patient was reported to have used a concomitant asthma medication other than a short-acting beta-agonist during the trial.

There were 20 departures from the protocol reported, however, only one was thought by the sponsor to have a potential impact on the trial. Predose FEV_1 for Patient #1 was 13.09 percent higher at Period 3 than at baseline, above the protocol-specified maximum of 10 percent. The remainder of departures concerned violations in protocol-defined time between treatment periods or the time of day at which exercise challenge was to be conducted. Patients 16 and 17 accounted for four of these departures each, with administration times for each treatment period consistently earlier than at baseline. These eight protocol departures do not appear to have substantial implications for the outcome of the trial. The remainder of protocol departures appear to be random and also appear unlikely to have had an impact on the analyses.

Efficacy Outcomes

There were no statistically significant differences among the **Mean Predose FEV_1** for the four treatment periods, recorded immediately prior to exercise challenge for each treatment group, as shown in Table 1.

Table 1: Predose FEV_1 Data
Mean (SD)

	Proventil HFA-134a	Proventil (CFC)	Ventolin	HFA-134a Placebo	P-value
FEV_1 (L)	3.43 (0.68)	3.41 (0.65)	3.40 (0.64)	3.44 (0.68)	0.610
FEV_1 as % of Predicted	87.4 (8.9)	87.1 (8.1)	86.6 (7.3)	87.8 (8.9)	0.624

There were seven efficacy outcomes reported by the sponsor. The primary efficacy endpoint was designated as the smallest percent change from predose FEV_1 during the post-exercise period.

1. Post-Exercise Smallest Percent Change from Predose FEV_1

This value was derived by selecting from the eight post-exercise timepoints for each patient/treatment combination the FEV_1 which reflected the smallest percent change from predose (smallest positive or largest negative percent change over the 90 minute post-exercise period). Individual data were averaged by treatment group and means for each treatment group were statistically compared, as previously described. This endpoint does not provide substantial information regarding the onset or duration of effect of the drug, i.e., the post-exercise timepoint from which the data were derived was variable and patient responses were not necessarily consistent throughout the 90 minute period. The outcomes are described in Table 2 on the following page.

Table 2: Smallest Change from Predose FEV_1 Efficacy Outcomes

	Proventil HFA	Proventil (CFC)	Ventolin	HFA-134a Placebo
Smallest Percent Change from Predose (%)				
Mean	2.0*	2.0*	3.6*	-23.7
SD	9.9	11.4	10.2	14.5
Median	2.9	2.2	2.6	-25.5
Min	-22.7	-19.8	-27.6	-56.4
Max	22.7	22.3	22.8	1.4
Smallest Change from Predose (L)				
Mean	0.06*	0.09*	0.12*	-0.79
SD	0.33	0.35	0.35	0.48
Min	-0.69	-0.52	-0.93	-1.84
Smallest Percent Change from Predose as Percent Predicted (%)				
Mean	1.7*	2.1*	3.2*	-20.3
SD	8.0	9.2	8.6	11.9
Min	-16.7	-14.5	-22.4	-44.2

* $p<.001$ from HFA-134a placebo.

This primary endpoint shows that each of the active treatments were significantly different from placebo, although there were no statistically significant differences among the active treatments. Response to active treatment were very similar and markedly different from the response to placebo. Given that percent change from predose was as low as minus 20 percent in each treatment group, it appears that not all patients were protected, by the sponsor's definition, from the effects of exercise by any of the treatments.

2. Post-Exercise Smallest Change from Predose FEV_1

As seen in Table 2 (above), each of the active treatments was statistically different from placebo. There were no statistically significant differences among the active treatments. These outcomes are consistent with the primary endpoint. The minimum smallest

change data appear to indicate that some patients in each treatment group did not experience a high degree of protection, as indicated by the primary endpoint.

3. Post-Exercise Smallest Percent Change from Predose FEV_1 as Percent of Predicted

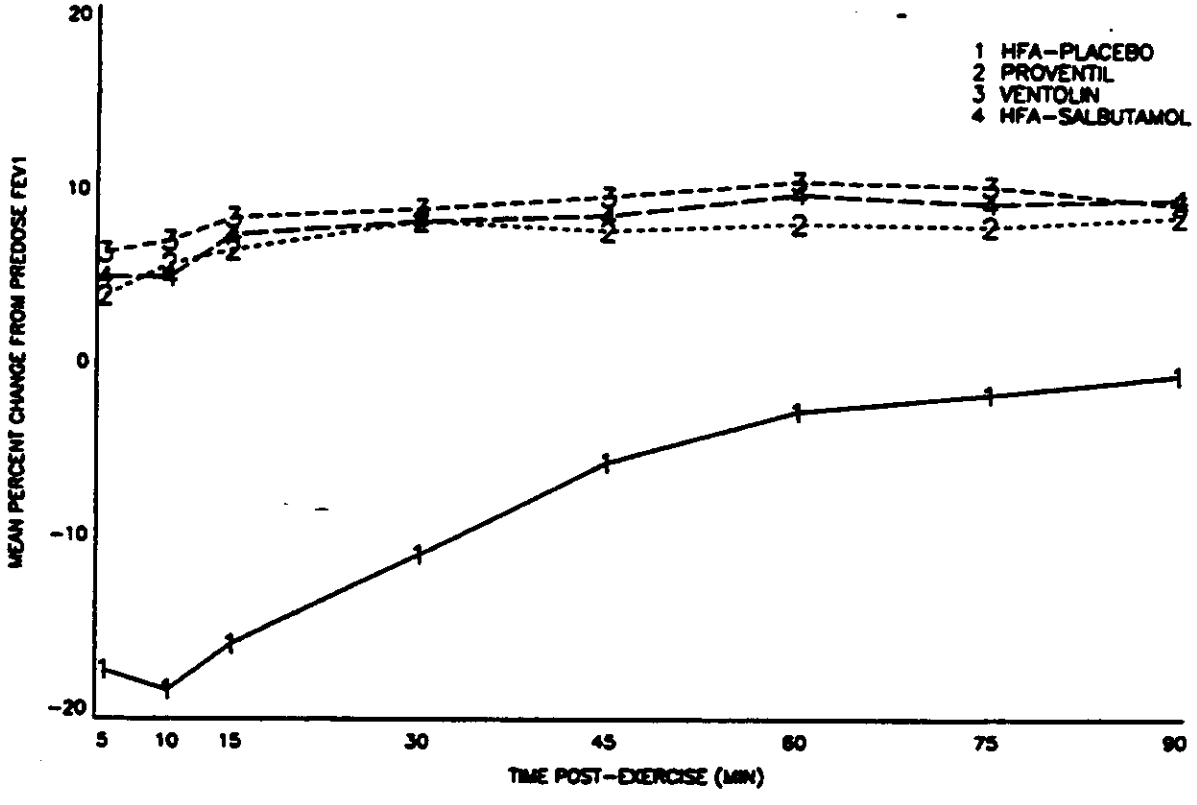
Table 2 (on the previous page) shows a response consistent with the previous endpoints, with no significant differences, among active treatments. All active treatments were significantly different than placebo, consistent with the primary endpoint.

4. Post-Exercise Mean Percent Change from Predose FEV_1

Figure 1 (below) depicts the mean percent change from predose for each treatment and timepoint. At each timepoint, all three active treatments were significantly different from placebo, but there were no significant differences among the active treatments.

FIGURE 1

Post-Exercise Mean Percent Change from Predose FEV_1



Patients in the active treatment groups were improved overall relative to predose at each timepoint, however, until approximately 30 minutes post-exercise the improvement relative to predose was increasing. Approximately 30 minutes post-exercise, the level of improvement appears to have reached a plateau and it appears that the effects of the active treatments were maintained throughout the 90 minute post-exercise observation period. Numerically, the mean data for Proventil HFA are essentially bounded by means for Proventil (CFC) and Ventolin, suggesting clinical comparability between Proventil HFA and the other active treatments.

Comment: The mean percent change profiles show that the nadir of effect of each treatment immediately followed the exercise challenge. Maximal responses occurred later, essentially during the time period in which active treatment responses were plateaued. The selection of smallest percent change in FEV_1 (including the most negative percent change) as a primary endpoint is more informative than the largest percent change endpoint originally proposed by the sponsor because it accurately captures minimum treatment effect despite the fact that the minimum effect was an improvement relative to predose FEV_1 for the active treatments.

The placebo treatment group means showed an expected decline in FEV_1 of nearly 20 percent relative to predose within 5 to 10 minutes post-exercise, then steady improvement to near baseline at the end of 90 minutes. These data help to confirm that the population selected for the trial appropriately showed exercise-induced bronchospasm. However, because the mean data failed to show a decline of more than 20 percent following exercise (maximum −18.9 at 10 minutes), the definition of "unprotected" patients as those who do exhibit a decline of 20 percent or more may be too stringent to show any separation among treatments, particularly among active treatments. It appears that there may be some value in examining the differences among treatments in the number of patients who responded with a decline of less than 10 percent, and between 10 and 20 percent from predose, as the sponsor's original protocol intended.

5. Post-Exercise Mean Change from Predose FEV_1

The mean change from predose FEV_1 ranged from 0.16 at 5 minutes post-exercise to 0.35 L and were fairly consistent among the three active treatment groups. The placebo group means showed a decline from predose at each timepoint, as much as 0.64L. Data from both the active and placebo groups appeared to be consistent with the mean percent change from predose findings.

6. Post-Exercise Mean Percent Change from Predose FEV_1 as Percent of Predicted

Mean percent change from predose FEV_1 as a percent of predicted were consistent with the other mean data efficacy endpoints. Active treatments improved between 3.8 and 9.0 percent above predose levels during the 90 minute post-exercise period and placebo means declined as much as 16.2 percent.

7. Number of "Protected" and "Unprotected" Patients

The number (percent) of patients whose FEV_1 decreased by less than or equal to 20 percent ("protected" patients), and whose FEV_1 decreased by more than 20 percent ("unprotected" patients) are shown in **bold** for each treatment group in Table 3 on the next page. Statistical analyses determined that each of the active treatment groups was significantly different than placebo.

The mean percent change from predose FEV_1 endpoint, described previously, showed that the maximum mean decline was 18.9 percent, in the placebo group. Only one patient in the active treatment groups reached a decline of 20 percent or more (Patient #1 responded in this manner to exercise challenge after both Proventil HFA and Ventolin treatment). Because categorical analysis conducted by the sponsor did not appear to provide a sensitive metric to distinguish among active treatments, Dr. Guo, the biometrics reviewer, provided a descriptive analysis of the number and percent of patients whose FEV_1 fell less than 10 percent from predose and those whose FEV_1 fell between 10 and 20 percent from predose. These values are also shown in Table 3 (not bolded). Although no statistical analyses were conducted, these data support the comparability of the active treatment groups and the differences between each active treatment and placebo.

Table 3: Number of "Protected" and "Unprotected" Patients

	Proventil HFA*	Proventil (CFC)*	Ventolin*	HFA-134a Placebo
> -10 Percent	18 (90%)	17 (85%)	19 (95%)	3 (15%)
≤ - 10 Percent to > -20 percent	1 (5%)	3 (15%)	0 (0%)	5 (25%)
> -20 Percent* ("Protected")	**19 (95%)**	**20 (100%)**	**19 (95%)**	**8 (40%)**
≤ -20 Percent* ("Unprotected")	**1 (5 %)**	**0 (0%)**	**1 (5%)**	**12 (60%)**

* Statistical analyses involved only two FEV_1 categories; $p<0.001$ from HFA-134a placebo.

Comment: Although all patients demonstrated a 20 percent decline in FEV_1 associated with exercise challenge during screening, i.e. were "unprotected," 40 percent of patients failed to exhibit the same response after treatment with the placebo formulation. This is depsite the fact that the placebo contains and that might be expected to increase airway reactivity. "Protection" by the placebo formulation was much less evident at the level of a 10 percent decline in FEV_1, as only 15 percent of placebo patients were "protected" at this level. It appears that assessment of patients who were "protected" and "unprotected" at the 10 percent level provides a more accurate characterization of the effects of treatment for this population.

Efficacy Conclusion

The biometrics reviewer, Dr. Ted Guo, provides in his review numerous graphical representations of these seven efficacy outcomes. Each of his depictions supports the numerical conclusions, as does his re-creation of the sponsor's primary analysis.

Overall, the data show that Proventil HFA provides clinically significant prophylaxis from exercise-induced bronchospasm in adults and children age 12 years of age and older when administered 30 minutes prior to exercise. Although the sensitivity of this trial to find differences among the active treatments is indeterminate, the data appear to suggest clinical comparability among the three active treatments.

Safety Outcomes

1. Adverse Events

There was one adverse event reported during treatment. Patient #15 experienced mild dizziness and lightheadedness with Proventil (CFC) five minutes into the exercise challenge. Her blood pressure and ECG were monitored and reported to be normal. Three other patients experienced adverse events during a washout period between treatments, including gastritis and aggravated allergy (Pt. #11), rhinitis (Pt. #12) and influenza (Pt. #19). The adverse event data do not appear to suggest a substantial difference in safety profiles among active treatments.

2. Vital Signs - Heart Rate, Systolic Blood Pressure & Diastolic Blood Pressure

No statistically significant differences were seen among predose assessments of these parameters for each treatment group. Post-dose comparison of treatment groups showed a maximum increase in mean **heart rate** of between 30 and 40 beats per minute. Proventil-HFA, Proventil and placebo groups performed similarly throughout the 90 minute post-exercise period, while the Ventolin group showed mean heart rates that were slightly greater than the other three groups. Statistically significant differences were seen between Ventolin and placebo at 15 and 60 minutes. Mean **systolic blood pressure** increased from baseline approximately 6 mm Hg more in the placebo group than in the active treatment groups, but no statistically significant differences were observed. Mean **diastolic blood pressure** was also increased from pre-dose during the post-exercise period for all treatments. No statistically significant differences were detected and there appears to be no clinically meaningful trend in the data. Overall, Proventil HFA did not show significant differences in vital sign parameters relative to placebo and the minimal variation observed among the active treatments do not appear to suggest clinically important differences.

3. 12-Lead Electrocardiogram – Ventricular Rate, PR Interval, QRS Interval, QT Interval and QT_c Interval

Mean **ventricular rate** was essentially unchanged after exercise in each treatment group, with maximum changes approximately 20 bpm above or below predose values. Mean **PR intervals** were also essentially unchanged, with a maximum increase of 32 msec associated with Ventolin treatment. The mean **QRS interval** was essentially unchanged in each group. The maximum increase from baseline **QT (uncorrected)** and QT_c interval among the treatment groups were 59 msec and 41 msec, respectively,

both associated with Proventil HFA treatment. Mean values for each parameter decreased approximately 5 to 10 msec in each group from predose. Overall, no statistically or clinically significant changes or trends are apparent in the ECG data.

4. Clinical Laboratory Tests

Pre- and post-study data were provided for each patient. Examination of the line listings revealed that none of the values appear to be indicative of clinically significant changes, confirming the investigator's assessment of the clinical implication of abnormal findings.

5. Physical Exams

"Abnormal" physical examination findings are reported for four patients. The findings are minor and consistent with the patient population enrolled in the trial. It is noted that Pt. #7 was reported to have had enlarged tonsils during the pre-study evaluation, but no post-study data are provided. Similarly, Pt. # 10 was reported to have "no wheezing" at the post-study evaluation, but no pre-study data are provided. While unlikely to have clinical implications, the sponsor should be asked to report the physical findings of each patient (even if patients are reported to be normal for all body sites), both pre- and post-study, as part of the auditing procedure in this review.

Safety Conclusion

The safety data from this trial comparing Proventil HFA to placebo show an acceptable safety profile, with minimal differences between treatments. Comparison of Proventil HFA with the other active treatments appear to support clinical comparability in regard to this indication. It does not appear that it will be necessary to add specific warnings, precautionary statements or adverse events to the currently approved labeling based on this trial.

Labeling Review

The sponsor has proposed two types of labeling changes; those specific to the EIB indication and updates related to the beta-agonist class labeling. Ms. Jani, the project manager, will review and comment on changes related to class labeling and any other differences between the previously approved version and the proposed version of the labeling.

Specific to the EIB claim, the sponsor has proposed to add a statement to the Clinical Trials section (line 84 of the sponsor's draft labeling) which states that "In another clinical study in adults, two inhalations of Proventil HFA (Albuterol Sulfate Inhalation Aerosol) taken 30 minutes before exercise prevented exercise-induced bronchospasm as demonstrated by the maintenance of FEV_1 within 80% of baseline values in the majority of patients." This statement is supported by the data submitted. It is also consistent with the currently approved Ventolin and Proventil (CFC) labeling, with the exception that both CFC products were studied with dosing approximately 15 minutes, rather than 30 minutes, prior to exercise.

The EIB trial submitted in this application evaluated response to 2 inhalations of treatment administered 30 minutes prior to exercise challenge. It did not directly assess time to onset of bronchoprotective effects by varying the interval between dosing and exercise challenge. However, the data submitted in support of the original NDA approval characterized the onset of Proventil HFA bronchodilatory effects as consistent with those of CFC comparators. In addition to numerous trials that established clinical and cumulative dosing comparability in the response to Proventil HFA, Ventolin and Proventil (CFC), Trials 1012-SILV and 1031-SILV specifically determined the onset of bronchodilation (defined as the time to a 15 percent increase from predose FEV_1) for both Proventil HFA and Ventolin to be approximately 6 minutes. These data suggest that the onset of bronchoprotective effect would be essentially the same among these three products and supports labeling for the Proventil HFA product that is consistent with Ventolin and Proventil (CFC). It is recommended that the Dosing and Administration section be modified to reflect that 2 inhalations should be administered ( ) 30 minutes before exercise.

Labeling for Ventolin and Proventil (CFC) further describes clinical trials conducted to assess the duration of prophylactic effect, as determined with repeated exercise challenge. No such studies were conducted in support of Proventil HFA and the statements are not transferable, since druation of effect may be particularly subject to differences in dose delivery.

It has been proposed that the Indications section (line 90) be modified to read "Proventil HFA (Albuterol Sulfate Inhalation Aerosol) is indicated in patients 12 years of age and older for the treatment or prevention of bronchospasm with reversible airway disease **and for the prevention of exercise induced bronchospasm.**" This change is acceptable.

Proposed changes to the Dosage and Administration section (line 340) include the statement "Exercise Induced Bronchospasm Prevention: the usual dose for adults age 12 years and older..." This statement should read "...adults **and children age** 12 years and older...", but is otherwise acceptable. It is also noted that the same modification should be made on line 334 for the general indication.

Audit Functions

Due to small size of this trial and the existence of supportive information from the original application, no clinical trial audit was requested from the Division of Scientific Investigations. There were no randomized patients who discontinued the study and no case report forms were required to be submitted. As described earlier, line listings have been reviewed for many of the parameters and the sponsor should be asked to provide complete information related to physical examination findings for each patient.

Conclusions

Efficacy outcomes, including smallest percent change from predose FEV_1, mean percent change from predose FEV_1 and a categorical analysis of degree of protective effect, show that Proventil HFA is effective relative to placebo.

Safety outcomes of this trial suggest minor systemic effects of Proventil HFA as compared to placebo, the nature of which are expected with an albuterol product in the enrolled population.

This trial was not powered to detect statistical differences among the active treatment groups and was conducted in mild asthmatic population that have been relatively insensitive to differences among active treatments. Clinical assessment of these data appear to confirm that Proventil HFA performs comparably to Proventil (CFC) and Ventolin.

Provided the issues listed below are adequately addressed, Proventil HFA may be approved for prevention of exercise induced bronchospasm in adults and children age 12 and older with a recommended dose of two inhalations 30 minutes prior to exercise.

Outstanding Issues

Ms. Jani, the Project Manager, will provide comments on the sponsor's proposed modifications related to beta-agonist class labeling and a comparison of the previously approved labeling with the current labeling (excluding EIB-related statements).

The following comments should be forwarded to the sponsor.

1. Please provide the complete line listings for pre- and post-study physical examination findings.

2. Lines 334 and 340 of the proposed labeling should be corrected to read "...adults and children age 12 years an older..."

3. Line 341 should be modified to read "...2 inhalations ( ) 30 minutes before exercise."

NOV 10 1997

MEDICAL OFFICER REVIEW

Division of Pulmonary Drug Products (HFD-570)

APPLICATION #: 20-503 **APPLICATION TYPE:** NDA

SPONSOR: 3M Pharmaceuticals **PRODUCT/PROPRIETARY NAME:** Proventil HFA

USAN / Established Name: Albuterol Sulfate Inhalation Aerosol

CATEGORY OF DRUG: Short Acting Beta-Agonist **ROUTE OF ADMINISTRATION:** Oral Inhalation

MEDICAL REVIEWER: Susan Johnson, Pharm.D. **REVIEW DATE:** November 7, 1997

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
9-22-97	9-26-97	Efficacy Supplement	Adult Exercise Induced Asthma

RELATED APPLICATIONS (if applicable)

Document Date:	APPLICATION Type:	Comments:

Overview of Application/Review:
This supplement is fileable.

Outstanding Issues:

Recommended Regulatory Action: Fileable

N drive location:

New Clinical Studies: _____ Clinical Hold _____ Study May Proceed

NDAs:

Efficacy / Label Supp.: _____ Approvable _____ Not Approvable

Signed: Medical Reviewer /S/ Date: 11/7/97

Medical Team Leader /S/ Date: 11/10/97

Submission Description

This supplement has been submitted in support of the addition of an indication in the prevention of exercise induced asthma for Proventil HFA in adults and children age 12 and older. The product was approved in August, 1996 and has been marketed since December, 1996. Proventil HFA is currently indicated for the "treatment of acute episodes of bronchospasm or prevention of asthmatic symptoms" in patients age 12 and above. The proposed dosage is 2 inhalations 30 minutes prior to exercise.

The sponsor has submitted a single clinical trial, 1150-SILV, entitled "Single-Dose Safety and Efficacy Study of HFA-134a Salbutamol Sulfate, Ventolin, Proventil and HFA-134a Placebo in Patients with Exercise-Induced Asthma." The principal investigator was Robert Dockhorn, M.D. Twenty mild-to-moderate asthmatic patients completed this four period crossover study. In each treatment period, patients received two inhalations of randomly assigned study drug, followed 30 minutes later by a treadmill exercise challenge test. Serial pulmonary function testing was conducted from pre-dose through 90 minutes after the exercise challenge. The primary efficacy endpoint was FEV_1 analyzed as the mean of the smallest percent change from baseline value recorded at any timepoint following the exercise challenge (i.e., the smallest positive or largest negative percent change over the 90 minute post-exercise period). Safety endpoints included adverse events, ECG changes, vital signs and physical and clinical laboratory evaluations.

No efficacy or safety data were submitted in addition to Trial 1150-SILV.

Filing Considerations

A single study was submitted in accordance with the division's "Points To Consider" document on development of oral inhalation products. The design of the trial, including treatment arms, number of subjects (N = 20) and procedures, appears adequate for review.

The inclusion criteria allowed enrollment of patients between the ages of 12 and 50; patients who completed the trial ranged in age from 14 to 43. The mean screening FEV_1 was 90 percent of predicted normal, with a range of 71 to 109 percent. Patients were enrolled if they demonstrated a 20 percent reduction in FEV_1 following exercise challenge. The study population adequately represents the labeling proposal.

The sponsor is currently submitting monthly updates regarding reports of blockage of the mouthpiece. As of October, 1997, there have been 131 U.S. reports of such events. As specified in the approval letter for this product, further CMC evaluation of this aspect of product performance was required and is ongoing. The review for this supplement should include consideration of potential problems in expanding the indications for this product, given unresolved CMC issues. These considerations do not preclude filing.

Review Issues

Further consideration will be given to the optimal FEV_1 parameter to use in the primary analysis. The conclusion on this issue will entail consideration of other therapeutic agents for both acute and chronic use.

Statistical analyses which compare active treatments will be necessary. These analyses may entail a comparison of the rate of "complete" versus "incomplete" success, i.e. those patients whose FEV_1 fell by less than five percent as compared to those whose FEV_1 fell by more than five percent during the post-exercise period.

Conclusion

This supplement is fileable.

No routine audit of this trial will likely be requested.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-503/S004

PHARMACOLOGY REVIEW(S)

Review of Pharmacology and Toxicology Data

Reviewer: VE Whitehurst

Division of Pulmonary Drug Products

HFD: HFD 570

Review completion date: August 10, 1998

NDA: NDA 20, 503

Review: Revised labeling

Information to be conveyed to the sponsor: Yes

Sponsor: 3M Pharmaceuticals
3M Center Bldg
St Paul, MN 55144-1000

Drug: (Proventil ^{R} HFA) (Albuterol Sulfate Inhalation Aerosol)

Chemical name: α^{i}-[(tert-butylamine) methyl)-4-hydroxy-α Xylene-, α,α^{1}-dial sulfate (2:1)-(salt).

Active agent: Albuterol sulfate

Dtug Class: Beta agonist

Indication: Treatment of reversible bronchospasm.

Administration : Oral inhalation

Introduction and history: Revised final labeling.

Labeling for Proventil HFA:

Clinical Pharmacology Section:

Preclinical:
Intravenous studies in rats with albuterol sulfate have demonstrated that albuterol crosses the blood–brain barrier and reaches brain concentrations amounting to approximately 5.0 % of the plasma concentrations. In structures outside the brain barrier (pineal and pituitary glands), albuterol concentrations were found to be 100 times those in the whole brain.

Line 47-49 should be moved and placed in the Pregnancy:Treatogenic section as shown below.

Lines [redacted] should be removed from the labeling. Information/data refer to propellant only.

Carcinogenesis, Mutagenesis and Impairment of Fertility:
In a 2-year study in Sprague-Dawley rats, albuterol sulfate caused a dose-related increase in the incidence of benign leiomyomas of the mesovarium at and above dietary doses of 2 mg/kg (approximately 10 times the maximum recommended inhalation daily dose for adults on a mg/m^2 basis). In another study this effect was blocked by the coadministration of propanolol, a non-selective beta adrenergic antagonist. In an 18-month study in CD-1 mice. albuterol sulfate showed no evidence of tumorigenicity at dietary doses up to 500 mg/kg (approximately 1700 times the maximum recommended inhalation daily dose for adults on a mg/m^2 basis). In a 22-month study in the Golden hamster, albuterol sulfate showed no evidence of tumorigenicity at dietary doses up to 50 mg/kg (approximately 230 times the maximum recommended inhalation daily dose for adults on a mg/m^2 basis).

Albuterol sulfate was not mutagenic in the Ames test with or without metabolic activation using tester strains S. typhurium TA 1537, TA 1538

and TA 98 or E coli WP_2, WP_{2uvra} and WP 67. No forward mutation was seen in yeast strain S.cerevisiae S9 nor any mitotic gene conversion in yeast strain S. cerevisiae JD_1 with or without metabolic activation. Fluctuation assays in S.typhurium, TA 98 and EcoliWP_2, both with metabolic activation, were negative. Albuterol sulfate was not clastogenic in a human peripheral lymphocyte assay or in an AH_1 strain mouse micronucleus assay at intraperitoneal doses up to 200 mg/kg.

Reproduction studies in rats revealed no impaired fertility at oral doses up to 50 mg/kg (approximately 340 times the maximum recommended inhalation daily dose for adults on a mg/m^2 basis).

Teratogenic Effects-Pregnancy : Category C

Albuterol sulfate has been shown to be teratogenic in mice. A study in CD-1 mice at subcutaneous doses (sc) at and above 0.25 mg/kg (less than the maximum recommended inhalation daily dose for adults on a mg/m^2 basis) showed cleft palate formation in 5 of 111 (4.5%) fetuses. A sc dose of 2.5 mg/kg/day (approximately 8 times the maximum recommended inhalation daily dose for adults on a mg/m^2 basis), induced cleft palate formation in 10 of 108 (9.3%) fetuses. The drug did not induce cleft palate formation at the low dose, 0.025 mg/kg/day (less than the maximum recommended inhation daily dose for adults on a mg/m^2 basis). Cleft palate also occurred in 22 of 72 (30.5%) fetuses from females treated with 2.5 mg/kg/day isoproterenol (positive control) administered subcutaneously (approximately 8 times the maximum recommended inhalation daily dose for adults on a mg/m^2 basis). A reproduction study in Stride Dutch rabbits revealed cranioschisis in 7 of 19 (37%) fetuses when albuterol sulfate was administered orally at 50 mg/kg (approximately 680 times the maximum recommended inhalation daily dose for adults on mg/m^2 basis).

In an inhalation reproduction study in Sprague-Dawley rats, albuterol sulfate/HFA 134 formulation did not exhibit any teratogenic effects at 10.5 mg/kg (approximately 70 times the maximum recommended inhalation daily dose for adults on a mg/m^2 basis).

There are no adequate and well-controlled studies in pregnant women. Albuterol should be used during pregnancy only if the potential benefits justifies the potential risk to the fetus.

During worldwide marketing experience, various congenital anomalies, including cleft palate and limb defects, have been rarely reported in the offspring of patients being treated with albuterol. Some of the mothers were taking multiples medications during their pregnancies. No consistent pattern of defects can be discerned, a relationship between albuterol use and congenital anomalies has not been established.

Overdosage:
The oral median lethal dose of albuterol sulfate in mice is greater than 2000 mg/kg (approximately 6800 times the maximum recommended inhalation daily dose for adults on a mg/m^2 basis). In mature rats, the subcutaneous median lethal dose of albuterol is approximately 450 mg/kg (approximately 3000 times the maximum recommended inhalation daily dose for adults on a mg/m^2 basis). In small young rats, the subcutaneous median lethal dose is approximately 2000 mg/kg (approximately 14000 times the maximum recommended inhalation daily dose for adults on a mg/m^2 basis). The inhalation median lethal dose has not been determined.

Drug: **Provential HFA**

	age	mg/dose	# daily doses	mg/day	kg	mg/kg	factor	mg/m²
Pediatric	[redacted]			0	3	0.00	25	0.00
Adult	>12	[redacted]	6	1.2	50	0.02	37	0.89

	Route	mg/kg/d	conv. factor	mg/m²	Dose Ratio Adults	Dose Ratio Children	Rounded Dose Ratio Adults	Rounded Dose Ratio Children
Carcinogenicity:								
mouse	[redacted]		3	1500	1689.19	---	#NAME?	---
mouse			3	0	---	---	---	---
mouse			3	0	---	---	---	---
rat	[redacted]		6	12	13.5135	---	#NAME?	---
hamster	[redacted]		4	200	225.225	---	#NAME?	---
Reproduction and Fertility:								
rat	[redacted]		6	300	337.838	N/A	#NAME?	N/A
rat			6	0	---	N/A	---	N/A
rat			6	0	---	N/A	---	N/A
extra			---	---	---	N/A	---	N/A
Teratogenicity:								
mouse	[redacted]		3	0.075	0.08446	N/A	1/12	N/A
mouse	[redacted]		3	0.75	0.84459	N/A	1/1	N/A
mouse	[redacted]		3	7.5	8.44595	N/A	#NAME?	N/A
rabbit	[redacted]		12	600	675.676	N/A	#NAME?	N/A
rat	[redacted]		6	63	70.9459	N/A	#NAME?	N/A
Overdosage:								
mouse	[redacted]		3	6000	6756.76	---	#NAME?	---
mouse			3	0	---	---	---	---
rat	[redacted]		6	2700	3040.54	---	#NAME?	---
rat	[redacted]		6	12000	13513.5	---	#NAME?	---
Other:	(Describe studies here)							
rat	[redacted]		6	0	---	---	---	---
rat			6	0	---	---	---	---
mouse			3	0	---	---	---	---

mouse	[redacted]	3	0	---	---	---	---
extra		---	---	---	---	---	---

Conversion, Correction, and Rounding Factors:

Human Age (yr)	Weight (kg)	Factor (kg/m²)	Species	Factor (kg/m²)	Exposure greater than x-times human	Round to nearest
0	3	25	dog	20	1	1
1	10	25	guinea pig	8	10	5
2	12	25	hamster	4	100	10
4	16	25	monkey	12	1000	100
6	20	25	mouse	3	10000	1000
12	50	37	rabbit	12		
			rat	6		

Recommendation: Reversions in the labeling should be conveyed to the sponsor.

/S/

Virgil Whitehurst
Pharmacologist 8-13-98

CC:
HFD-570/HSheevers
HFD-570/ VWhitehurst
HFD-570/PJani

/S/ 8/13/98

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Draft

Labeling

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-503/S004

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION
CLINICAL STUDIES

AUG 17 1998

Date	
NDA #	20-503
Applicant	3M Pharmaceuticals
Name of Drug	Proventil® HFA (Albuterol/Salbutamol Sulfate) Inhalation Aerosol
Indication	Prevention of exercise induced asthma
Document Reviewed	• Sponsor's cover letter dated September 22, 1997 • Clinical study 1150-SILV (Vol. 4 – vol. 6) • Efficacy Data as SAS data file: Efficacy.sd2
Statistical Reviewer	Ted (Ji-Yang) Guo, Div II/OEB, HFD-715
Medical Input	Dr. Sue Johnson, ODE II, HFD-570

Table of Contents

Summary

Based on the evaluation of the primary efficacy variable: the smallest percent change in FEV1, this reviewer concludes:

- The crossover study conducted by the sponsor was based on an appropriate study plan.
- The carry-over effect from one treatment period to the next was not statistically significant.
- The differences in the smallest percent change in FEV1 between the active treatments and the placebo were statistically significant.
- The differences in the smallest percent change in FEV1 among the active treatments were negligible. Therefore, the proposed Proventil HFA-134a demonstrated efficacy comparable to Proventil and Ventolin.

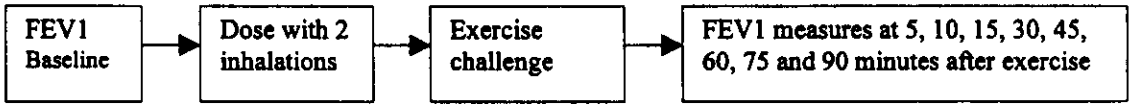
In summary, the added indication for treating exercise-induced asthma for Proventil HFA is well supported by the sponsor's statistical evidence based on *NDA 20-503, Proventil HFA Supplement for Exercise Induced Asthma Indication (vols. 4-6)*. Proventil HFA provides a successful protection against exercise-induced decline in FEV1. Its effectiveness is similar to that of either Proventil of Ventolin.

Introduction

The sponsor proposed that Proventil HFA-134a (Albuterol/Salbutamol[1] sulfate Inhalation Aerosol) is an effective substitute for the CFC-bearing Proventil® indicated for exercise-induced asthma. A phase 2 clinical study, #1150-SILV was submitted by the sponsor to support the efficacy claim. The proposed market dose for patients, 12 years of age and older is 2 inhalations every 4 to 6 hours (pp.24, vol. 4), delivering a dose of 108 mcg Albuterol sulfate. This study (#1150-SILV) was a:

- Randomized,
- Single-blind,
- Four-period,
- Crossover,
- Phase II study during 6/26/95-10/19/95 (final report issued 3/21/96), using
- Twenty patients, including 7 females and 13 males, comprising 80% (16/20) Caucasians, age 14-43 years of age, all having
- Exercise-induced asthma (EIA), treated with
- HFA-134a salbutamol sulfate, Proventil®, Ventolin®, and HFA Placebo.

The entire study comprised 4 study periods that lasted about 2 hours each and were set apart by 3-10 days. During each period, each patient received one from the four treatments after pre-dosing. The patients self-administered 2 inhalations, according to the study protocol. The study procedure is described in the following diagram:



Baseline FEV1 was measured about 45 minutes before dosing while exercise was performed about 30 minutes after dosing. The above procedure was repeated for the following period 3-10 days later.

The primary efficacy variable was based on the percentage change in FEV1 from baseline value. The goal was to evaluate the protection against exercise-induced fall in FEV1. The baseline FEV1 was the pre-dose, pre-exercise measurement. The percentage change was defined by

$$[(\text{Post Exercise Measurement} - \text{Baseline Measurement})/\text{Baseline Measurement}]\times 100$$

The post-exercise FEV1 was expected to be smaller than the pre-exercise one. If one treatment was more effective than the other was, this treatment was expected to have a smaller decline in FEV1. The sponsor decided that the primary efficacy variable be the smallest percentage change in FEV1.

[1] Albuterol sulfate in the official generic name in the U.S., while the WHO recommended name is salbutamol sulfate (pp. 10. Vol. 4)

Sponsor's Conclusions

The following points summarize the sponsor's analysis:

- The smallest percent change in FEV1 from baseline was used as the primary efficacy variable
- "There were no significant differences between treatments with respect to the pre-dose FEV1 values (p=0.610)... (pp. 112, vol. 4)"
- "The study results indicate that the three active treatments, HFA-134a salbutamol sulfate, Proventil, and Ventolin, were similar in terms of efficacy and each were significantly superior to HFA-134a placebo in preventing bronchospasm in patients with exercise-induced asthma. (pp. 80, vol. 4)"

In this report, this reviewer evaluated the sponsor's conclusions (based on data, *Efficacy.sd2*), paying close attention to the efficacy claim.

Evaluation of Study Design

Described in the above introductory section, this study was a 4-period crossover design. Each patient was randomly assigned to one of the following treatment sequences (Table 1). In this report, Salbutamol, Proventil, Ventolin, and HFA-Placebo are denoted as treatment #1, #2, #3, and #4, respectively. These numbers in Table 1 are placed in parentheses.

Table 1. Treatment Sequence (Randomization Plan)

Sequence	Period #1	Period #2	Period #3	Period #4
1	Salbutamol sulfate (1)	Ventolin® (3)	Placebo (4)	Proventil® (2)
2	Ventolin®(3)	Proventil® (2)	Salbutamol sulfate (1)	Placebo (4)
3	Placebo (4)	Salbutamol sulfate (1)	Proventil® (2)	Ventolin® (3)
4	Proventil® (2)	Placebo (4)	Ventolin® (3)	Salbutamol sulfate (1)

Table 2 describes the treatments patients actually received for the 4 periods. This was a balanced design. The 20 patients were assigned to treatments according to the following 5 Latin squares.

Table 2. Treatments Patients Received

Treatments Received			
[redacted]			
1	3	4	2
2	4	3	1
4	1	2	3
3	2	1	4
[redacted]			
1	3	4	2
3	2	1	4
2	4	3	1
4	1	2	3
[redacted]			

A Latin Square

Reviewer's Remarks

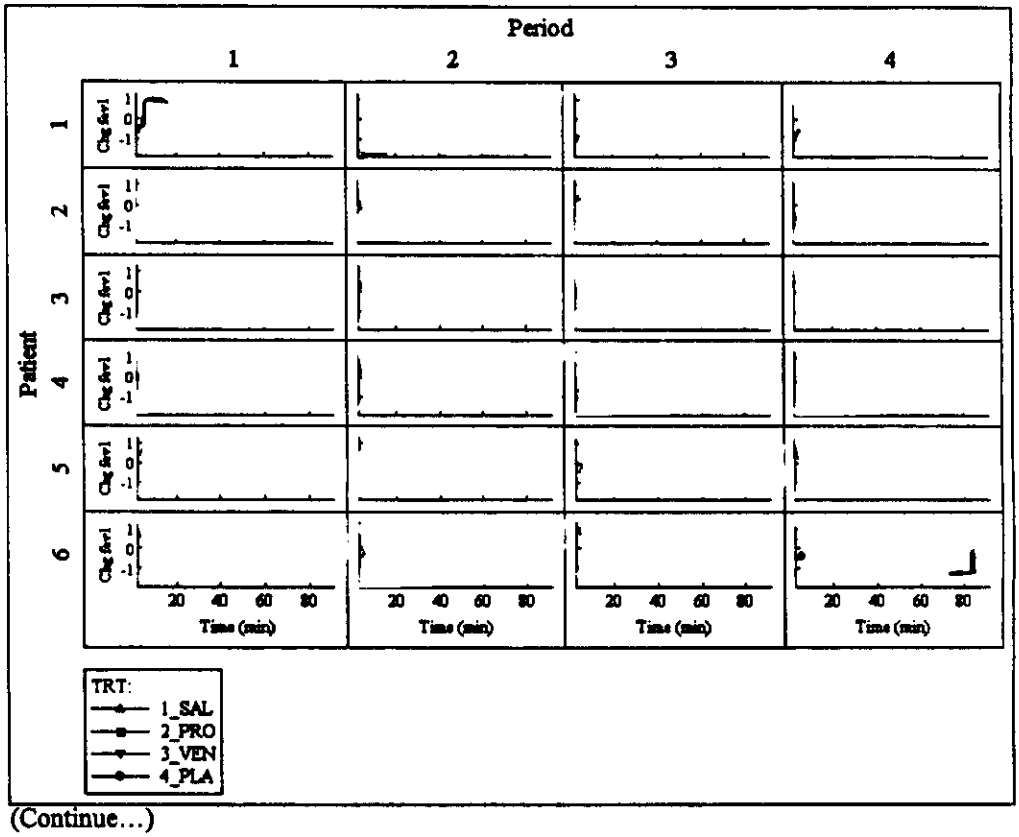
Selection of primary efficacy variable: The smallest percentage change in FEV1

Note that repeated measurements were taken on each patient at several time points for each period. Repeated measurements can contain useful information on the form of the carry-over effect, should one exist. However, because the measurements on the same patient were correlated, and the analysis of repeated measurements lies in their covariance structure (which in most cases was unknown), one makes certain assumptions on the covariance structure to use the common ANOVA. Johns and Kenward[i] point out, "Arguably the single most important approach is the one in which the repeated measurements from each individual are reduced to a few summary statistics which can be analyzed separately using standard univariate techniques..." In this trial, the smallest percentage change in FEV1 represented the worst outcome in comparing the treatment differences, therefore was considered to be an appropriate selection of efficacy indicator. Senn[ii] presents an example of a similar crossover design in which the lowest number of FEV1 after exercise challenge was adopted as the outcome variable. This reviewer considers the design reasonable and adequate.

Descriptions of FEV1

The changes in FEV1 from pre-exercise measurements at every time point by patient by period are described in Figure 1. The purpose for these graphs was to observe an overall picture of the percent changes in FEV1 for all the patients in the study. The descriptions on the individual-patient-level demonstrated that, overall; the 5-90 minute measurements resembled roughly a horizontal trend. In many cases, the first 20-minute measurements showed a greater change (i.e., reduction in FEV1) than later time. This, therefore, supported that the use of the smallest percent change in FEV1 as the primary outcome variable was reasonable.

Figure 1. FEV1 changes from pre-exercise measurements



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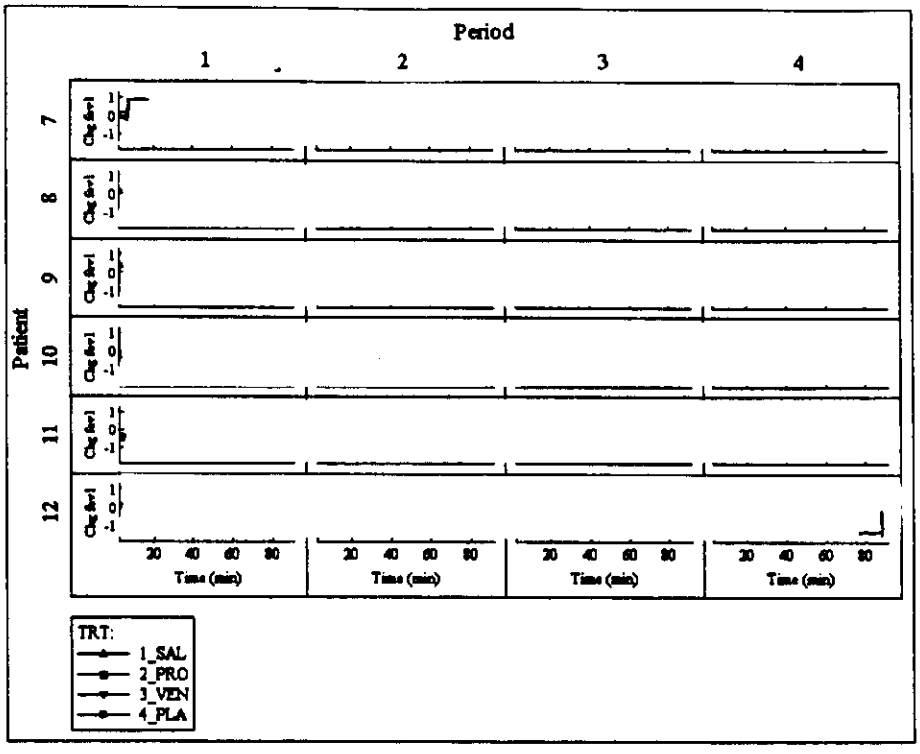
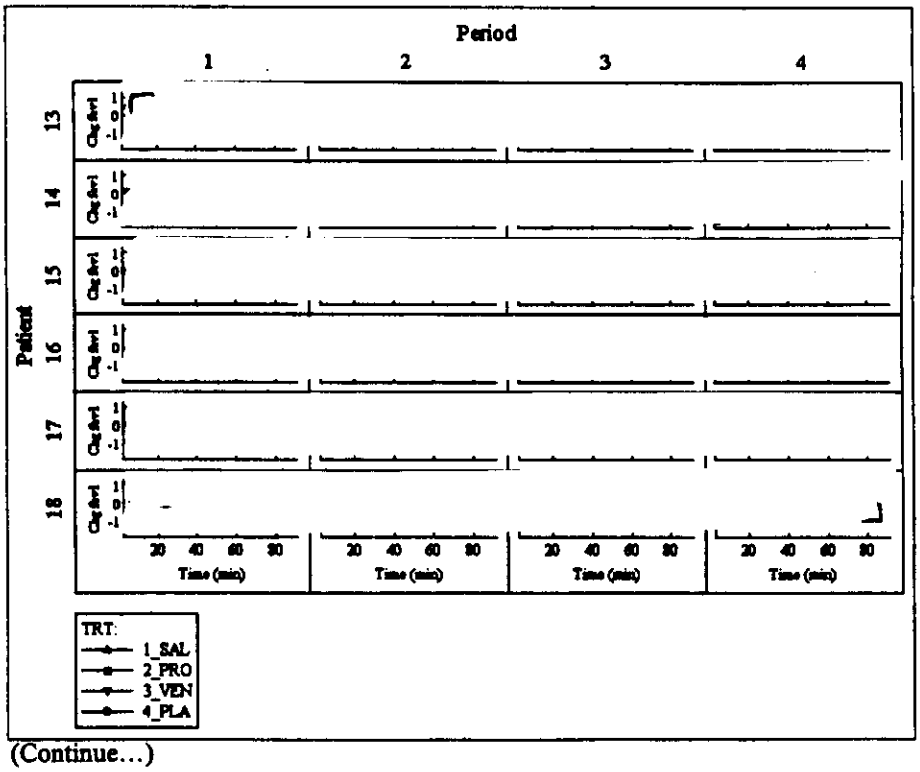
(Figure 1 continued)





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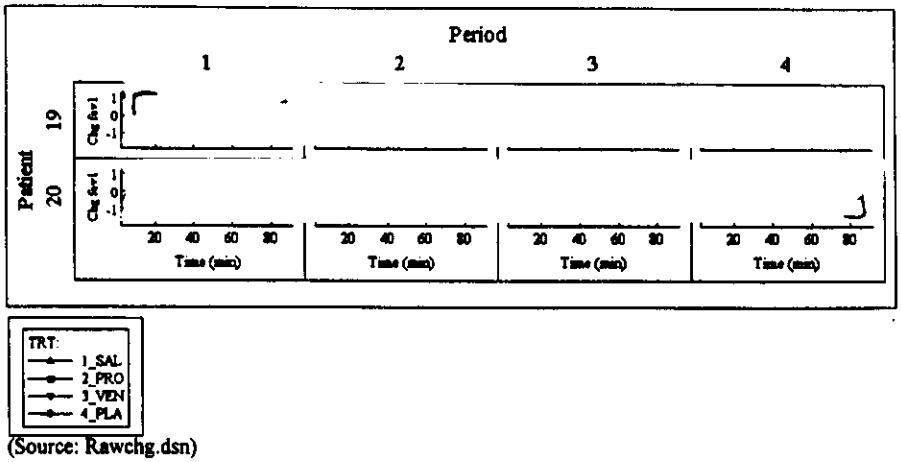
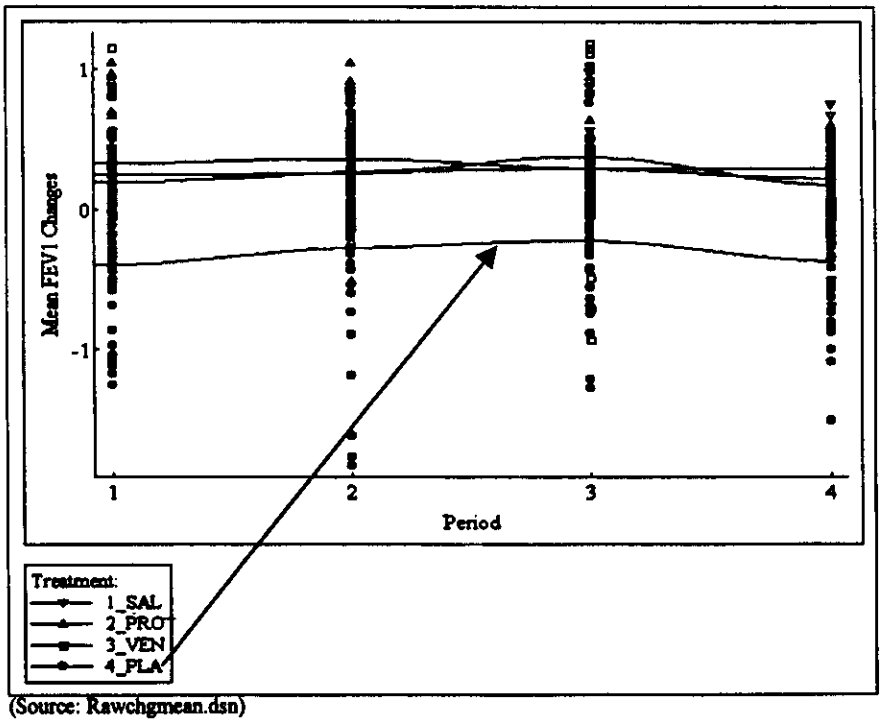
(Figure 1 continued)



(Source: Rawchg.dsn)

Figure 2 demonstrates FEV1 changes from pre-exercise measurements broken down by treatment. Greater reductions were observed when patients received placebo than when receiving active treatments. Observing the fitted curves[2], the distinctions between the active treatments and the placebo were clear, but the differences among the active treatments were not distinguishable. In this graph, all observations are used.

Figure 2. FEV1 changes from pre-exercise measurements



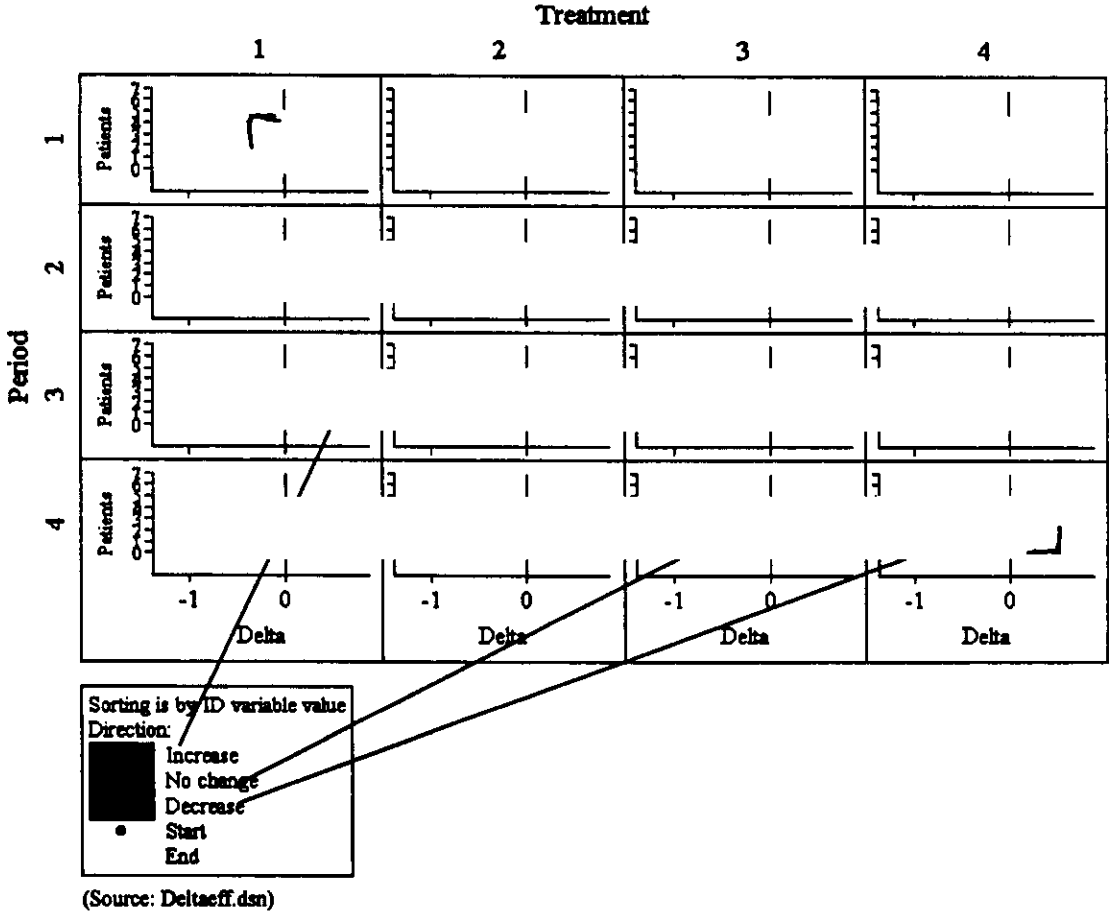
(Source: Rawchgmean.dsn)

[2] The fitted curves were draw using a kernel density function with 20 data points and the default smoothing factor of 7.

The primary efficacy variable was the smallest percent change in FEV1 over the time points (0-90 minute observations). For changes having negative values, such changes represent the greatest drop from pre-dosing measurements.

Considering the data based on the smallest percent change in FEV1 alone, Figure 3 describes the changes in FEV1 for every individual patient, by period, by treatment. In Figure 3, the horizontal lines mark the pre- and post-exercise FEV1 values. Note that the 20 patients are labeled on the vertical axis (the patient numbering is not relevant). The treatments 1-4 represent Proventil HFA, Proventil, Ventolin, and Placebo, respectively. Note that those patients while treated with placebo experienced a much greater decline in post-exercise FEV1 than when received active treatments.

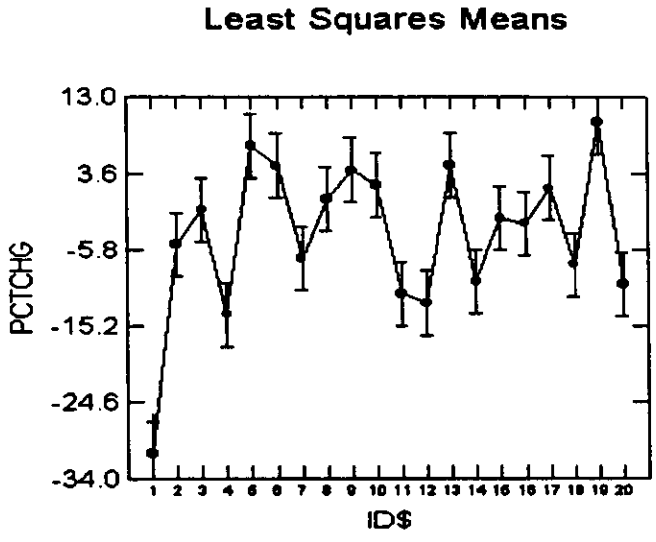
Figure 3. Changes in FEV1 for individual patients



(Source: Deltaeff.dsn)

Figure 4 depicts the means (averaged over the treatments) of the smallest percent change in FEV1 from pre-exercise for individual patients. Patient #1 had a distinctively low value, indicating that this patient was really different compared with others.

Figure 4. Smallest percent change in FEV1 from pre-exercise: Individual means



(Source: Systat 6.1 run)

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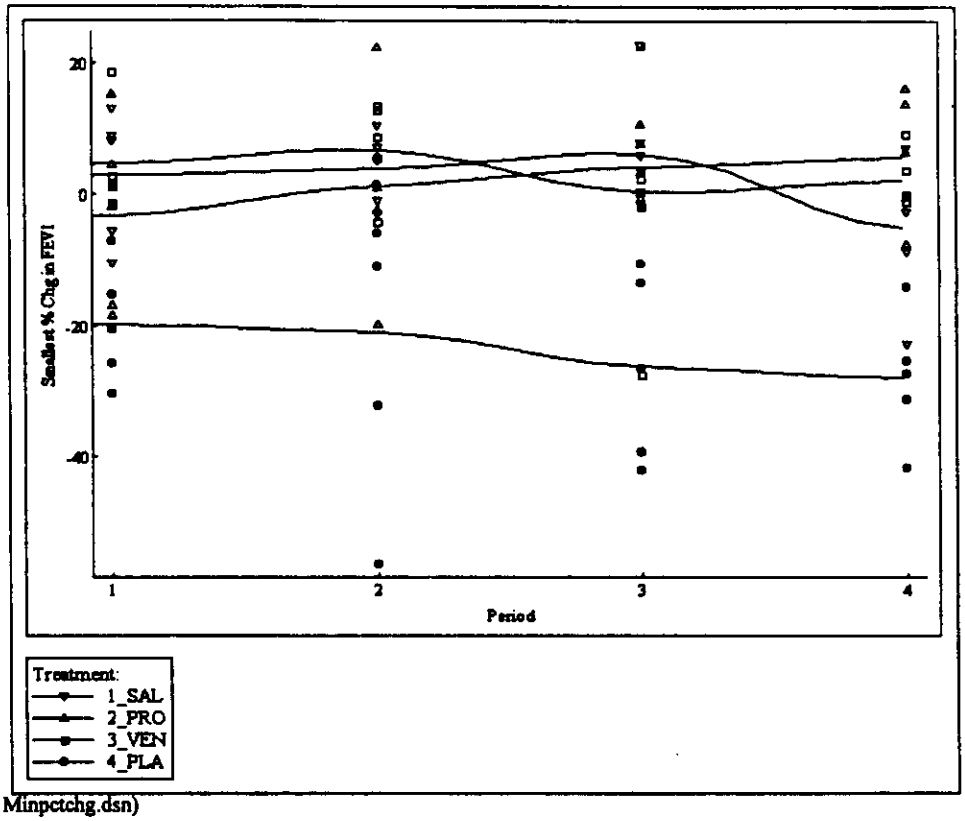
Figure 5 below demonstrates the smallest percent changes in FEV1 from pre-exercise measurements over time by treatment group. The lines are the quadratic regression fit of the points. This graph shows a clear difference between the active treatments and the placebo, and the differences among the active treatments are small.

Figure 5. The smallest percent changes in FEV1 from pre-exercise



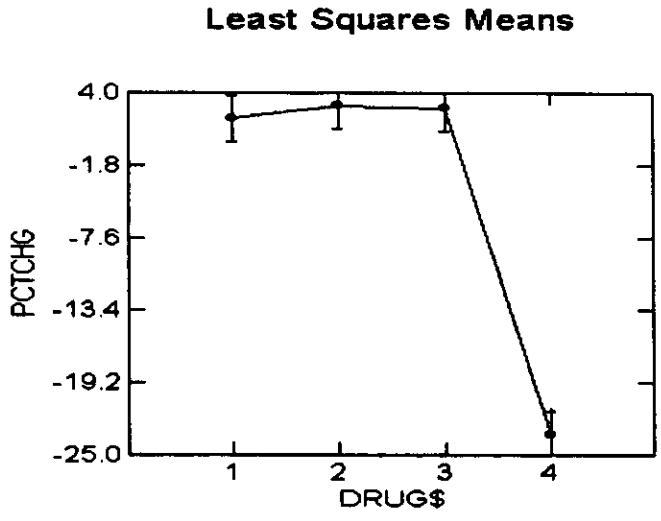
(Source: Minpctchg.dsn)

Note that, in Figure 5, there are 20 data points for each period, representing the 20 patients. Each patient received a different treatment (including placebo) from one period to the next. Therefore, the measurements on the same patient that was observed over time were correlated.

Both Figure 2 and Figure 5 above have demonstrated that the differences among the active treatments were negligible compared to the differences between the active treatments and the placebo. This finding indicated that, with the active treatments, the patients' demonstrated a higher FEV1 level after exercise compared with when treated with the placebo.

Figure 6 shows the least square means of the smallest percent changes in FEV1 from pre-exercise measurements by treatment group (produced by *Systat 6.1*). Treatment #4 represents the placebo, while #1, #2, and #3 are HFA salbutamol sulfate, Proventil, and Ventolin, respectively. The differences among the active treatments appear to be very small compared to the placebo.

Figure 6. Smallest percent change in FEV1 from pre-exercise by treatment



(Systat 6.1 graph)

Figure 7 lists, among other statistics, the means of the smallest percent changes in FEV1, by treatment group. The mean values shown here match the sponsor's report (Table 2, pp. 40, vol. 4).

Figure 7. Numerical descriptions of the smallest percent changes in FEV1

PCTCHG

Treatment	Mean	SD	Median	IQR	Min	Max
1_SAL	1.98	9.85	2.86			
2_PRO	2.01	11.38	2.20			
3_VEN	3.57	10.20	2.61			
4_PLA	-23.75	14.53	-25.54			

9.39 14.37 19.36

(Source: Descstats.dsn)

In the figure, IQR represents *interquartile range*, the distance between the 25th and the 75th sample percentiles. The means and medians indicated a generally smaller percent change for placebo.

The above graphical descriptions of FEV1 lead to the following statistical analysis.

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Analysis of the Crossover Study

The statistical method for this crossover study this reviewer adopted is described by Joseph L. Fleiss[iii]. The majority of the statistical calculations were done using software, ***Systat 6.1 for Windows***. The following tests were performed:

- Test of significance of the carryover effect;
- Test of significance of the treatment's direct effect.
- If the treatment's direct effect is found significant, then an additional Dunnett's Test for the differences between all the active treatments and the placebo is performed.

In Table 3, is the resulting ANOVA from *Systat 6.1* run:

Table 3. ANOVA of Crossover Study

Analysis of Variance

Source	Sum-of-Squares	df	Mean-Square	F-ratio	P
ID	6654.751	19	350.250	5.716	0.000
DRUG	9193.881	3	3064.627	50.013	0.000
PERIOD	201.081	3	67.027	1.094	0.360
RESIDUAL (CARRY)	330.404	3	110.135	1.797	0.159
Error	3125.117	51	61.277		

The conclusions are based on Table3 and summarized in the following highlights:

- The carryover (from one treatment period to the next) effect was not statistically significant (p=0.159).
- The treatment's direct effect was found statistically significant. The F-statistic used for this test was 50.01, greater than the critical value of 2.15 based on the F-distribution with degrees of freedom of 3 and 51.
- The Dunnett's Test indicated that the means of all the three active treatments were statistically significantly greater than that of the placebo.
- In addition, Figures 2 and 3 clearly demonstrated that the differences in the smallest percent change in FEV1 among the active treatments were very small and indistinguishable.

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Conclusions

Based on the evaluation of the primary efficacy variable: the smallest percent change in FEV1, this reviewer concludes:

- The crossover study conducted by the sponsor was based on an appropriate study plan;
- The carry-over effect from one treatment period to the next was not statistically significant;
- The differences in the smallest percent change in FEV1 between the active treatments and the placebo were statistically significant;
- The differences in the smallest percent change in FEV1 among the active treatments were negligible. Therefore, the proposed Proventil HFA-134a resembles the same efficacy as that of Proventil and Ventolin.

In conclusion, the added indication for treating exercise-induced asthma for Proventil HFA is well supported by the sponsor's statistical evidence. Proventil HFA provides a successful protection against exercise-induced decline in FEV1. Its effectiveness is similar to that of either Proventil of Ventolin.

Signoff Page

Statistical Reviewer: Ji-Yang (Ted) Guo, Ph.D. /S/ 8/15/98

Concur: Steve Wilson, Ph.D. /S/ 8/14/98
S. Edward Nevius, Ph.D. /S/ 8/17/98

CC:
Archival NDA 20-503

HFD-570/Division file
HFD-570/SJohnson
HFD-570/Pjani

HFD-715/Division file
HFD-715/SWilson
HFD-715/TGuo

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File: N20503.doc

References

[i] Jones, Byron and Kenward, Michael. Design and Analyses of Cross-Over Trials. 6.1. Chapman and Ha 1989: 242-47. ll
[ii] Senn. Cross-over Trials in Clinical Research. 5.3. John Wiley & Sons 1993: 125.
[iii] Fleiss, Joseph L. The Design and Analysis of Clinical Experiments. 10.3. John Wiley & Sons 1986: 281-9.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-503/S004

CORRESPONDENCE

Clinical Team Leader Review Memorandum

***Memorandum to*:**	**NDA 20-503 file**
Product:	**Proventil HFA EIB efficacy supplement**
Memo date:	**9-9-98**
Memo from:	**Robert J. Meyer, MD Medical Team Leader, DPDP**

This memorandum is to document the Medical Team Leader secondary review conclusions on the exercise-induced bronchospasm efficacy supplement for Proventil HFA. The secondary review was carried out both concurrently with and subsequent to Dr. Johnson's primary clinical review. This memorandum will be brief, as Dr. Johnson' review covers the main issues well.

***Overview*:**

The CFC-formulations of albuterol (Ventolin and Proventil) carry an indication for exercise-induced bronchospasm, Ventolin for patients ages 4 and above, Rroventil has no age mentioned in the Indications section, but rather clarifies a dosing recommendation for 12 and above in the dosage and Administration section. This supplement is for the EIB claim for Proventil HFA in patients ages 12 and above. Proventil HFA was approved in August of 1996 for the treatment of bronchospasm in patients ages 12 and above. The pediatric supplement (covering both EIB and relief of bronchospasm) was recently submitted and is under review.

***Efficacy*:**

In keeping with the Division's Points to Consider document on inhalation drug development, the sponsor submitted a single well-controlled study to gain this indication. The study was a comparison to placebo (HFA-134a) and to both Ventolin Inhalation Aerosol and Proventil Inhalation Aerosol (CFC) – Study 1150-SILV. This was a single dose, evaluator blind, four-period cross-over study. All three active formulations convincingly protected against EIB in this 20 patient study by any analysis, and few signals of important differences were detected. If one considers a categorical analysis of response (<10% fall in FEV_1; >=10% but <20%; and >= 20%), the three actives appear to have comparable distributions, with 85 – 95% of subjects having a less than 10% drop in FEV_1 as opposed to only 15% in the placebo subjects. On average, the active treatment patients' FEV_1s rose following exercise, rather than falling. An unfortunate lapse in this study design which would have rendered the results even more meaningful is the lack of any assessment of duration of effect (i.e., no repeat exercise testing more remote from dosing). However, the data do support the efficacy of Proventil HFA in preventing EIB when used as a single dose and suggest relative comparability to the marketed CFC brand name inhalers (though the study design allows no definitive judgements in this regard).

Safety:

The safety data in this supplement are, by design, minimal and speak mainly to tolerability and very short-term safety. No signals of important safety issues or differences between the HFA and CFC formulations arose.

Overall Conclusions:

I am in agreement with Dr. Johnsons assessment that this application is approvable from the clinical standpoint. The dosing recommendations for Proventil HFA should be aligned with existing labeling for the CFC products to the extent possible given the data generated.

Recommendation:

I recommend approval of this product, once all labeling issues are resolved. I do not see any phase 4 commitments being necessary from the clinical standpoint.

Robert J. Meyer, MD 9/9/98
Medical Team Leader
Division of Pulmonary Drug Products

cc: Johnson/Medical Officer/HFD-570
Meyer/Medical Team Leader/HFD-570
Jani/project manager/HFD-570
Division File/HFD-570
NDA #20-503

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3M Pharmaceuticals
3M Center Building 260-6A-22
St.Paul, MN 55144-1000

SUPPL NEW CORRESP

(612) 736-2083

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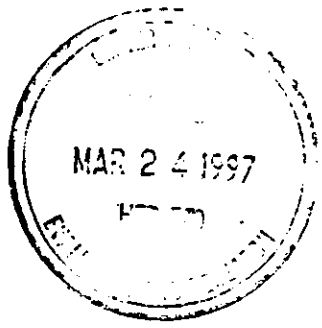
3M

March 21, 1997



Division of Pulmonary Drug Products (HFD-570)
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room 10B-03
5600 Fishers Lane
Rockville, MD 20857

Subject: **NDA 20,503 Proventil® HFA**
(Albuterol Sulfate Inhalation Aerosol)
Supplement: Amendment of Patent Information

Dear Sir/Madam:

Please find a copy of a letter from Mr. Ted Ringsred of 3M Intellectual Property Counsel which amends the patent information for Proventil HFA (See Attachment #1).
A copy of the patent information which was previously submitted in support of 3M Pharmaceuticals' new drug application is supplied in Attachment #2 for your reference.
This information is sent in compliance with the requirements set forth under FDCA 505(b)(1) and 21 CFR 314.53 (c)

This submission is sent in duplicate with a separate desk copy for Parinda Jani. If you have any questions regarding this submission, please contact me at (612) 736-2083.

Sincerely,

Marlene V. Peterson

Marlene V. Peterson
Sr. Regulatory Coordinator

Attachments

cc: Mary Ann Hollovak
Drug Information Services Branch
and
Central Document Room
Park Building, Room 2-14

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Ted K. Ringsred
Intellectual Property Counsel

Office of Intellectual
Property Counsel

March 21, 1997

3M

Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Re: TIME SENSITIVE PATENT INFORMATION

To Whom It May Concern:

This information is submitted in compliance with FDCA § 505(b)(1) and 21 CFR §314.53(c) in order to amend and supplement the previous submission of patent information in connection with the application for approval of Proventil HFA™ albuterol sulfate metered dose inhaler product.

The undersigned declares that U.S. Patent No. 5,225,183 covers the formulation, composition, and/or method of use of Proventil HFA™ albuterol sulfate metered dose inhaler product. This product is currently approved under Section 505 of the Federal Food, Drug, and Cosmetic Act.

The undersigned declares that U.S. Patent No. 5,439,670 covers the formulation, composition, and/or method of use of Proventil HFA™ albuterol sulfate metered dose inhaler product. This product is currently approved under Section 505 of the Federal Food, Drug, and Cosmetic Act.

The undersigned declares that U.S. Patent No. 5,605,674 covers the formulation, composition, and/or method of use of Proventil HFA™ albuterol sulfate metered dose inhaler product. This product is currently approved under Section 505 of the Federal Food, Drug, and Cosmetic Act.

Sincerely,

Ted Ringsred

Ted K. Ringsred
Office of Intellectual Property Counsel
Intellectual Property Counsel

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