CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 17-559/S023
19-383/S010
17-853/S016

APPROVAL LETTER

NDA 17-559/S-023

NOV -9 1998

Schering Corporation
2000 Galloping Hill Road
Kenilworth, New Jersey 07033-0530

Attention: Joseph F. Lamendola, Ph.D.
Vice President
U.S. Regulatory Affairs

Dear Dr. Lamendola:

Please refer to your supplemental new drug application dated December 23, 1996, received December 24, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Proventil (albuterol) Inhalation Aerosol.

We acknowledge receipt of your submissions dated January 3, 1997, and September 24, 1998. Your submission of September 24, 1998, constituted a full response to our June 24, 1997, action letter.

Reference is also made to the October 28, 1998, telephone conversation between Mr. James Walker of your company with Ms. Parinda Jani of this Division.

The supplement provides for revised labeling as requested by the Agency for all beta-agonists used for asthma and/or COPD.

We have completed the review of this supplemental application, as amended, and it is approved effective on the date of this letter.

As agreed to by Mr. Walker, the term "test spray" in the DOSAGE AND ADMINISTRATION section, and in the Patient's Package Insert will be more clearly defined based on the data. A "prior approval" supplement will be submitted within 6 months of the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed marked-up draft labeling.

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 17-559/S-023." Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of the labeling may be required.

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

APPEARS THIS WAY
ON ORIGINAL

DIV File

~~NDA 17-853/S-016~~
NDA 19-383/S-010

Schering Corporation
2000 Galloping Hill Road
Kenilworth, New Jersey 07033-0530

NOV 6 1998

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Vice President
U.S. Regulatory Affairs

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We acknowledge receipt of your submissions dated January 3, 1997 and September 24, 1998. Your submissions of September 24, 1998, constituted a full response to our June 24, 1997, action letters.

These supplemental new drug applications provide for revised labeling as requested by the Agency for all beta-agonists used for asthma and/or COPD.

We have completed the review of these supplemental applications, as amended, and they are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed marked-up draft labeling.

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 supplements NDA 17-853/S-016 and NDA 19-383/S-010." Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drugs become available, revision of the labeling may be required.

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Director
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Enclosure

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ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 17-559/S023
19-383/S010
17-853/S016

FINAL PRINTED LABELING

(1)

BEST POSSIBLE COPY

S 2 4 5 8 7 1 2

f:
17559 Rc'd. 8/26/94
iby:

PHARMACIST
TEAR AT PERFORATION
GIVE TO PATIENT

F-19529320 1573

PROVENTIL®
brand of albuterol, USP
Inhalation Aerosol
FOR ORAL INHALATION ONLY

PROVENTIL®
brand of albuterol, USP
Inhalation Aerosol

FOR ORAL INHALATION ONLY

Patient's Instructions For Use

Figure 1

Figure 2

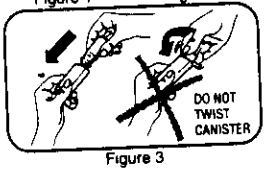


Figure 3

Before using your PROVENTIL Inhalation Aerosol, read complete instructions carefully.

1. SHAKE THE INHALER WELL immediately before each use. **Then remove the cap from the mouthpiece. Check mouthpiece for foreign objects prior to use.** Make sure the canister is fully and firmly inserted into the actuator. The PROVENTIL Inhalation Aerosol canister should only be used with the yellow PROVENTIL Inhalation Aerosol mouthpiece. This yellow mouthpiece should not be used with any other inhalation drug product. Similarly, the canister should not be used with other mouthpieces.

2. As with all aerosol medications, it is recommended to "test spray" into the air before using for the first time and in cases where the aerosol has not been used for a prolonged period of time.

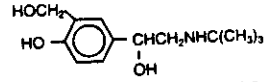
3. BREATHE OUT FULLY THROUGH THE MOUTH, expelling as much air from your lungs as possible. Place the mouthpiece fully into the mouth, holding the inhaler in its upright position (See Figure 1) and closing the lips around it.

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. Before breathing out, remove [illegible] and release

NTIL INHALATION AEROSOL OR REFILL DISPENSED

DESCRIPTION The active component of PROVENTIL Inhalation Aerosol is albuterol, USP racemic α^1-[(*tert*-butylamino)methyl]-4-hydroxy-*m*-xylene-α,α'-diol), a relatively selective beta$_2$-adrenergic bronchodilator, having the chemical structure:



The molecular weight of albuterol is 239.3, and the empirical formula is $C_{13}H_{21}NO_3$. Albuterol is a white to off-white crystalline solid. It is soluble in ethanol, sparingly soluble in water, and very soluble in chloroform. The World Health Organization recommended name for albuterol base is salbutamol.

PROVENTIL Inhalation Aerosol is a pressurized metered-dose aerosol unit for oral inhalation. It contains a microcrystalline suspension of albuterol in propellants (trichloromonofluoromethane and dichlorodifluoromethane) with oleic acid. Each actuation delivers 100 mcg albuterol, USP from the valve and 90 mcg of albuterol, USP from the mouthpiece. Each 17.0 g canister provides 200 oral inhalations.

CLINICAL PHARMACOLOGY The primary action of beta-adrenergic drugs, including albuterol, is to stimulate adenyl cyclase, the enzyme which catalyzes the formation of cyclic-3',5'-adenosine monophosphate (cyclic AMP) from adenosine triphosphate (ATP) in beta-adrenergic cells. The cyclic AMP thus formed mediates the cellular responses. Increased cyclic AMP levels are associated with relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

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 in 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.

In controlled clinical trials, albuterol has been shown 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 agonist drugs, can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, symptoms, and/or ECG changes.

Albuterol is longer acting than isoproterenol in most patients by any route of administration because it is not a substrate for the cellular uptake processes for catecholamines nor for catechol-*O*-methyl transferase.

The effects of rising doses of albuterol and isoproterenol aerosols were studied in volunteers and asthmatic patients. Results in normal volunteers indicated that the propensity for increase in heart rate for albuterol is ½ to ¼ that of isoproterenol. In asthmatic patients similar cardiovascular differentiation between the two drugs was also seen.

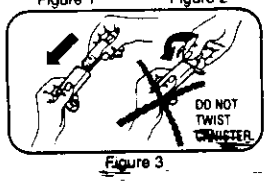
Preclinical: Intravenous studies in rats with albuterol sulfate have demonstrated that albuterol crosses the blood-brain barrier and reaches brain concentrations that are amounting to approximately 5.0% of the plasma concentrations. In structures outside the blood-brain barrier (pineal and pituitary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

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 beta-agonists and methylxanthines are administered concurrently. The clinical significance of these findings is unknown.

Pharmacokinetics: Because of its gradual absorption from the bronchi, systemic levels of albuterol are low after inhalation at recommended doses.

Administration of tritiated albuterol by inhalation to four subjects resulted in maximum plasma concentrations within 2 to 4 hours. Due to the insensitivity of the assay method, the metabolic rate and half-life of elimination of albuterol in plasma could not be determined. However, data from urinary excretion studies indicated that albuterol has an elimination half-life of 3.8 hours. Approximately 72% of the [illegible]

Figure 1 Figure 2



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2. As with all aerosol medications, it is recommended to "test spray" into the air before using for the first time and in cases where the aerosol has not been used for a prolonged period of time.

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 1) 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. Before breathing out, remove the inhaler from your mouth and release your finger from the canister.

6. Wait one minute and SHAKE the inhaler again. Repeat steps 2 through 4 for each inhalation prescribed by your physician.

7. CLEANSE THE INHALER THOROUGHLY AND FREQUENTLY. Remove the metal canister and cleanse the plastic case and cap by rinsing thoroughly in warm running water, at least once a day. After thoroughly drying the plastic case and cap, gently replace the canister downward into the case **without using a twisting motion.** (See Figure 3.) Replace the cap.

DOSAGE: Use only as directed by your physician.

The correct amount of medication in each inhalation cannot be assured after 200 actuations from the 17.0 g canister 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 specified 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 Inhalation Aerosol without consulting your physician.

WARNINGS: The action of PROVENTIL Inhalation Aerosol may last up to 6 hours or longer. PROVENTIL Inhalation Aerosol should not be used more frequently than recommended. Do not increase the dose or frequency of PROVENTIL Inhalation Aerosol without consulting your physician. If you find that treatment with PROVENTIL Inhalation Aerosol becomes less effective for symptomatic relief, your symptoms become worse, and/or you need to use the product more frequently than usual, you should seek immediate medical attention. While taking PROVENTIL Inhalation Aerosol, other asthma drugs and inhaled medicines should be used only as prescribed by your physician.

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. Keep out of reach of children. Avoid spraying in eyes.

Store between 15°and 30°C (59°and 86°F). Failure to use the product within this temperature range may result in improper dosing. Shake well before using. For optimal results, the canister should be at room temperature before use.

GIVE PATIENT'S INSTRUCTIONS TO PATIENT THIS LEAFLET SHOULD ACCOMPANY EACH PROVENTIL INHALATION AEROSOL OR REFILL DISPENSED

100 mcg albuterol. Each [illegible] from the mouthpiece. Each 17.0 g canister provides 200 oral inhalations.

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

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Pharmacokinetics: Because of its gradual absorption from the bronchi, systemic levels of albuterol are low after inhalation at recommended doses.

Administration of tritiated albuterol by inhalation to four subjects resulted in maximum plasma concentrations within 2 to 4 hours. Due to the insensitivity of the assay method, the metabolic rate and half-life of elimination of albuterol in plasma could not be determined. However, data from urinary excretion studies indicated that albuterol has an elimination half-life of 3.8 hours. Approximately 72% of the inhaled dose is excreted in the urine within 24 hours, 28% as unchanged drug and 44% as metabolite.

Clinical Trials: In controlled clinical trials the onset of improvement in pulmonary function was within 15 minutes, as determined by both maximal midexpiratory flow rate (MMEF) and FEV_1. MMEF measurements also showed that near maximum improvement in pulmonary function generally occurs within 60 to 90 minutes, following 2 inhalations of albuterol and that clinically significant improvement generally continues for 3 to 4 hours in most patients. In clinical trials, some patients with asthma showed a therapeutic response (defined by maintaining FEV_1 values 15% or more above baseline) which was still apparent at 6 hours. Continued effectiveness of albuterol was demonstrated over a 13-week period in these same trials.

In clinical studies, 2 inhalations of albuterol taken approximately 15 minutes prior to exercise prevented exercise-induced bronchospasm, as demonstrated by the maintenance of FEV_1 within 80% of baseline values in the majority of patients. One of these studies also evaluated the duration of the prophylactic effect to repeated exercise challenges, which was evident at 4 hours in the majority of patients, and at 6 hours in approximately one third of the patients.

INDICATIONS AND USAGE PROVENTIL Inhalation Aerosol is indicated in patients 12 years of age and older, for the prevention and relief of bronchospasm in patients with reversible obstructive airway disease, and for the prevention of exercise-induced bronchospasm.

CONTRAINDICATIONS PROVENTIL Inhalation Aerosol is contraindicated in patients with a history of hypersensitivity to albuterol or any of its components.

WARNINGS **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 Inhalation Aerosol than usual, this may be a marker of destabilization of asthma and requires re-evaluation of the patient and the treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment, eg, corticosteroids.

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.

Paradoxical Bronchospasm: PROVENTIL Inhalation Aerosol can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs, PROVENTIL 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 or vial.

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

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

PRECAUTIONS **General:** Albuterol, 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, hyperthyroidism, 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 and could be expected to occur in some patients after use of any beta-adrenergic bronchodilator.

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Store between 15°and 30°C (59°and 86°F). Failure to use the product within this temperature range may result in improper dosing. Shake well before using. For optimal results, the canister should be at room temperature before use.

Note: The indented statement below is required by the Federal government's Clean Air Act for all products containing or manufactured with chlorofluorocarbons (CFCs).

This product contains dichlorodifluoromethane (CFC-12) and trichloromonofluoromethane (CFC-11), substances which harm the environment by destroying ozone in the upper atmosphere.

Your physician has determined that this product is likely to help your personal health. USE THIS PRODUCT AS DIRECTED, UNLESS INSTRUCTED TO DO OTHERWISE BY YOUR PHYSICIAN. If you have any questions about alternatives, consult with your physician.

Schering Corporation
Kenilworth, NJ 07033 USA

PHARMACIST — DETACH HERE ◆ AND GIVE PATIENT'S INSTRUCTIONS TO PATIENT THIS LEAFLET SHOULD ACCOMPANY EACH PROVENTIL INHALATION AEROSOL O

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Paradoxical Bronchospasm: PROVENTIL Inhalation Aerosol can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs, PROVENTIL 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 or vial.

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PRECAUTIONS **General:** Albuterol, 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, hyperthyroidism, 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 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 pre-existing 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: The action of PROVENTIL Inhalation Aerosol may last up to 6 hours or longer. PROVENTIL Inhalation Aerosol should not be used more frequently than recommended. Do not increase the dose or frequency of doses of PROVENTIL Inhalation Aerosol without consulting your physician. If you find that treatment with PROVENTIL Inhalation Aerosol becomes less effective for symptomatic relief, your symptoms become worse, and/or you need to use the product more frequently than usual, you should seek medical attention immediately. While you are using PROVENTIL Inhalation Aerosol, other inhaled drugs and asthma medications should be taken only as directed by your physician. Common adverse effects include palpitations, chest pain, rapid heart rate, tremor, or nervousness. If you are pregnant or nursing, contact your physician about the use of PROVENTIL Inhalation Aerosol. Effective and safe use of PROVENTIL Inhalation Aerosol includes an understanding of the way that it should be administered. See illustrated **Patient's Instructions For Use.**

The contents of PROVENTIL Inhalation Aerosol are under pressure. Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 120°F may cause bursting. Never throw container into fire or incinerator. Keep out of reach of children. Avoid spraying in eyes.

Drug Interactions: Other short-acting sympathomimetic aerosol bronchodilators should not be used concomitantly with albuterol. If additional adrenergic drugs are to be administered by any route, they should be used with caution to avoid deleterious cardiovascular effects.

Beta Blockers: Beta-adrenergic receptor blocking agents not only

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DOSAGE: Use only as directed by your physician.

The correct amount of medication in each inhalation cannot be assured after 200 actuations from the 17.0 g canister 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 specified 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 Inhalation Aerosol without consulting your physician.

WARNINGS: The action of PROVENTIL Inhalation Aerosol may last up to 6 hours or longer. PROVENTIL Inhalation Aerosol should not be used more frequently than recommended. Do not increase the dose or frequency of PROVENTIL Inhalation Aerosol without consulting your physician. If you find that treatment with PROVENTIL Inhalation Aerosol becomes less effective for symptomatic relief, your symptoms become worse, and/or you need to use the product more frequently than usual, you should seek immediate medical attention. While taking PROVENTIL Inhalation Aerosol, other asthma drugs and inhaled medicines should be used only as prescribed by your physician.

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. Keep out of reach of children. Avoid spraying in eyes.

Store between 15°and 30°C (59°and 86°F). Failure to use the product within this temperature range may result in improper dosing. Shake well before using. For optimal results, the canister should be at room temperature before use.

Note: The indented statement below is required by the Federal government's Clean Air Act for all products containing or manufactured with chlorofluorocarbons (CFCs).

This product contains dichlorodifluoromethane (CFC-12) and trichloromonofluoromethane (CFC-11), substances which harm the environment by destroying ozone in the upper atmosphere.

Your physician has determined that this product is likely to help your personal health. USE THIS PRODUCT AS DIRECTED, UNLESS INSTRUCTED TO DO OTHERWISE BY YOUR PHYSICIAN. If you have any questions about alternatives, consult with your physician.

Schering Corporation
Kenilworth, NJ 07033 USA

19529320 Rev. 8/99

PHARMACIST — DETACH HERE ◆ AND GIVE PATIENT'S INSTRUCTIONS TO PATIENT — THIS LEAFLET SHOULD ACCO

values in the majority of patients. One of these studies also evaluated the duration of the prophylactic effect to repeated exercise challenges, which was evident at 4 hours in the majority of patients, and at 6 hours in approximately one third of the patients.

INDICATIONS AND USAGE PROVENTIL Inhalation Aerosol is indicated in patients 12 years of age and older, for the prevention and relief of bronchospasm in patients with reversible obstructive airway disease, and for the prevention of exercise-induced bronchospasm.

CONTRAINDICATIONS PROVENTIL Inhalation Aerosol is contraindicated in patients with a history of hypersensitivity to albuterol or any of its components.

WARNINGS **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 Inhalation Aerosol than usual, this may be a marker of destabilization of asthma and requires re-evaluation of the patient and the treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment, eg, corticosteroids.

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.

Paradoxical Bronchospasm: PROVENTIL Inhalation Aerosol can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs, PROVENTIL 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 or vial.

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

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

PRECAUTIONS **General:** Albuterol, 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, hyperthyroidism, 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 and could be expected to occur in some patients after use of any beta-adrenergic bronchodilator.

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Drug Interactions: Other short-acting sympathomimetic aerosol bronchodilators should not be used concomitantly with albuterol. If additional adrenergic drugs are to be administered by any route, they should be used with caution to avoid deleterious cardiovascular effects.

Beta Blockers: Beta-adrenergic receptor blocking agents not only block the pulmonary effect of beta-agonists, such as PROVENTIL 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 be considered, although they should be administered with caution.

Diuretics: The ECG changes and/or hypokalemia that 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.

Digoxin: Mean decreases of 16% to 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 this finding 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.

Monoamine Oxidase Inhibitors or Tricyclic Antidepressants: Albuterol 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 vascular 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 and above dietary doses of 2.0 mg/kg (approximately 15 times the maximum recommended daily inhalation dose for adults on an mg/m² basis). In another study this effect was blocked by the coadministration of propranolol, a nonselective 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 daily inhalation dose for adults on an mg/m² 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 daily inhalation dose for adults on an mg/m² 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.

Reproduction studies in rats demonstrated no evidence of impaired fertility at oral doses of albuterol sulfate up to 50 mg/kg (approximately 340 times the maximum recommended daily inhalation dose for adults on an mg/m² basis).

Teratogenic Effects—Pregnancy Category C: Albuterol sulfate has been shown to be teratogenic in mice. A study in CD-1 mice at subcutaneous (sc) doses at and above 0.25 mg/kg (approximately equal to the maximum recommended daily inhalation dose for adults on an mg/m² basis), induced cleft palate formation in 5 of 111 (4.5%) fetuses. At an sc dose of 2.5 mg/kg (approximately 8 times the maximum recommended daily inhalation dose for adults on an mg/m² basis) albuterol sulfate induced cleft palate formation in 10 of 108 (9.3%) fetuses. The drug did not induce cleft palate formation when administered at an sc dose of 0.025 mg/kg (significantly less than the maximum recommended daily inhalation dose for adults on an mg/m² 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.

A reproduction study in Stride Dutch rabbits revealed cranioschisis in 7 of 19 (37%) fetuses when albuterol sulfate was administered orally at a dose of 50 mg/kg (approximately 680 times the maximum recommended daily inhalation dose for adults on an mg/m² basis).

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

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, albuterol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

During worldwide marketing experience, 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 has not been established.

Use in Labor and Delivery—Use in Labor: Because of the potential for beta-agonist interference with uterine contractility, use of PROVENTIL 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 preterm labor. The benefit:risk ratio when albuterol is administered for tocolysis has not been established. Serious adverse reactions, including maternal pulmonary edema, have been reported during or following treatment of premature labor with $beta_2$-agonists, including albuterol.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because of the potential for tumorigenicity shown for albuterol in some animal studies, 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.

Pediatric Use: Safety and effectiveness in children below the age of 12 years have not been established.

ADVERSE REACTIONS The adverse reactions of albuterol are similar in nature to those of other sympathomimetic agents, although the incidence of certain cardiovascular effects is less with albuterol.

Percent Incidence of Adverse Reactions in Patients ≥ 12 Years of Age in a 13-Week Clinical Trial* (n=147)

Adverse Event	PROVENTIL Inhalation Aerosol	Isoproterenol Inhaler
Tremor	< 15	< 15
Nausea	< 15	< 15
Tachycardia	10	10
Palpitations	< 10	< 15
Nervousness	< 10	< 15
Increased Blood Pressure	< 5	< 5
Dizziness	< 5	< 5
Heartburn	< 5	< 5

*A 13-week, double-blind study compared albuterol and isoproterenol aerosols in 147 asthmatic patients.

Cases of urticaria, angioedema, rash, bronchospasm, hoarseness, oropharyngeal edema, and arrhythmias (including atrial fibrillation, supraventricular tachycardia, and extrasystoles) have also been reported after the use of inhaled albuterol. In addition, albuterol, like other sympathomimetic agents, can cause adverse reactions such as hypertension, angina, vomiting, vertigo, central nervous system stimulation, insomnia, headache, unusual taste, 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, angina, hypertension, tachycardia with rates up to 200 beats per minute, nervousness, headache, tremor, dry mouth, palpitation, nausea, dizziness, and insomnia. In addition, seizures, hypotension, arrhythmias, fatigue, malaise, and hypokalemia may also occur. As with all sympathomimetic aerosol medications, cardiac arrest and even death may be associated with abuse of PROVENTIL Inhalation Aerosol. Treatment consists of discontinuation of PROVENTIL 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 bron-

clearly outweigh the risk.

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The oral median lethal dose of albuterol sulfate in mice is greater than 2000 mg/kg (approximately 6800 times the maximum recommended daily inhalation dose for adults on an 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 an 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 and children on an mg/m^2 basis). The inhalation median lethal dose has not been determined in animals.

DOSAGE AND ADMINISTRATION *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; in some patients, 1 inhalation every 4 hours may be sufficient. More frequent administration or a larger number of inhalations is not recommended. For maintenance therapy or prevention of exacerbation of bronchospasm, 2 inhalations, 4 times a day should be sufficient.

The use of PROVENTIL Inhalation Aerosol can be continued as medically indicated to control recurring bouts of bronchospasm. During this time most patients gain optimal benefit from regular use of the inhaler. Safe usage for periods extending over several years has been documented.

If a previously effective dosage regimen fails to provide the usual response, 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.

Exercise-Induced Bronchospasm Prevention: The usual dosage for adults and children 12 years and older is 2 inhalations, 15 minutes prior to exercise. For treatment, see above.

It is recommended to "test spray" PROVENTIL Inhalation Aerosol into the air before using for the first time and in cases where the aerosol has not been used for a prolonged period of time.

HOW SUPPLIED PROVENTIL Inhalation Aerosol, 17.0 g canister contains 200 metered inhalations, box of one (NDC 0085-0614-02). Each actuation delivers 100 mcg of albuterol from the valve and 90 mcg of albuterol from the mouthpiece. Each canister is supplied with a yellow plastic actuator with orange dust cap, and Patient's Instructions.

PROVENTIL Inhalation Aerosol REFILL canister, 17.0 g, contains 200 metered inhalations, with Patient's Instructions; box of one (NDC 0085-0614-03).

The correct amount of medication in each inhalation cannot be assured after 200 actuations from the 17.0 g canister even though the canister is not completely empty. The canister should be discarded when the labeled number of actuations have been used.

Store between 15° and 30°C (59° and 86°F). Failure to use the product within this temperature range may result in improper dosing. For optimal results, the canister should be at room temperature before use. Shake well before using.

PROVENTIL Inhalation Aerosol canister should be used only with the actuator provided. The yellow actuator should not be used with other aerosol medication canisters.

Note: The indented statement below is required by the Federal government's Clean Air Act for all products containing or manufactured with chlorofluorocarbons (CFCs).

> **WARNING:** Contains dichlorodifluoromethane (CFC-12) and trichloromonofluoromethane (CFC-11), substances which harm public health and the environment by destroying ozone in the upper atmosphere.

A notice similar to the above WARNING has been placed in the "Patient's Instructions for Use" portion of this package insert under the Environmental Protection Agency's (EPA's) regulations. The patient's warning states that the patient should consult his or her physician if there are questions about alternatives.

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If a previously effective dosage regimen fails to provide the usual response, 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.

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It is recommended to "test spray" PROVENTIL Inhalation Aerosol into the air before using for the first time and in cases where the aerosol has not been used for a prolonged period of time.

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Schering Corporation
Kenilworth, NJ 07033 USA

Rev. 8/99

8-19529320

JUN 24 1997

PROJECT MANAGER'S LABELING REVIEW

NDA: 17-559/S-017, S-019, S-020, S-023

PROJECT MANAGER: Parinda Jani

DRUG: PROVENTIL INHALATION AEROSOL

SPONSOR: SCHERING CORP.

SUBMISSION DATES: **January 3, 1989 (S-017)**
June 1, 1989 (S-017)
November 9, 1993 (S-019)
November 19, 1993 (S-019)
February 25, 1994 (S-019)
APRIL 14, 1995 (S-020)
December 23, 1996 (S-023)
January 3, 1997 (amendment S-023)

Supplement S-017 provides for a revised HOW SUPPLIED and Patient's Instruction for Use sections.

The amendment to supplement S-017 also provides for revised established name and changes to the DESCRIPTION section.

Supplement S-019 provides for changes to the package insert and PPI as per EPA final regulation 58 FR 8136, dated February 11, 1993 (warning for CFC containing products).

Amendment to Supplement S-019 provides for revised subsection Pregnancy: Teratogenic Effects: Pregnancy Category C of the PRECAUTIONS section. A new paragraph regarding various congenital anomalies, including cleft palate and limb defects is added at the end of the subsection

Supplement S-020 provides for revised Drug Interactions subsection of the PRECAUTIONS section. Statement regarding drug-interaction between albuterol and digoxin, and lowering of serum potassium are added.

Supplement S-023 provides for the changes recommended by the Division under Beta-agonist Class labeling.

The last approved labeling supplement on file is S-010, approved April 22, 1986. All the labeling changes recommended for albuterol products were submitted in annual reports instead of

supplements to the NDA.

The product name is revised throughout the package insert to "Proventil Inhalation Aerosol" as recommended by the Division.

DESCRIPTION:

The word "racemic" is added as recommended by the Division (S-017 amendment). There are no other changes made to this section.

CLINICAL PHARMACOLOGY:

The second paragraph, "In-Vitro and in-vivo studies....is not yet established." was added in supplement S-020 (This was the first paragraph). It is revised in supplement S-023 to be consistent with other Proventil products.

The third paragraph, " In controlled clinical trials,....and/or ECG changes." was added in S-020.

The forth paragraph is same as previous labeling.

The fifth paragraph, "The effect of rising doses...was also seen." is revised.

The deleted paragraph,

The paragraph under Preclinical heading is revised as recommended by the Agency.

Pharmcokinetics data for all the Proventil formulations are included under "Pharmacokinetics" heading.

The paragraphs under Clinical Trials heading used to be in INDICATION AND USAGE section. It is appropriate to move these paragraphs under Clinical Trials heading.

INDICATION AND USAGE:

The second paragraph is moved under the heading "Clinical Trials" in CLINICAL PHARMACOLOGY section. This change is appropriate. Also, Proventil MDI is only approved for patients 12 years of age and older

CONTRAINDICATIONS:

There are no changes made to this section.

WARNINGS:

This section is completely revised as recommended in the beta-agonist class labeling document.

PRECAUTIONS-General:

This section needs to be revised as follows so as to be consistent with other albuterol products.

> Albuterol, 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, hyperthyroidism, 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 [redacted] 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 pre-existing 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.

PRECAUTIONS-Information for Patients, and Drug Interactions:

These sections are completely revised as recommended in the beta-agonist class labeling document. The PRECAUTION regarding The MAO inhibitors and tricyclic antidepressant under the Drug Interactions subsection has been revised to current recommendations.

PRECAUTIONS-Carcinogenesis, Mutagenesis, Impairment of Fertility, and Teratogenic Effects-Pregnancy Category C sections:

The referenced animal doses to human doses are converted to X times maximum recommended human daily dose on a mg/m^2 basis. These changes needs to be verified by a pharmacologist.

PRECAUTIONS-Use in Labor and Delivery:

This section is revised as recommended by the Agency.

PRECAUTIONS-Nursing Mothers:

There are no changes made to this section.

PRECAUTIONS-Pediatric Use:

Since Proventil MDI is not approved for children under the age of 12 years [redacted]

ADVERSE REACTIONS:

The sponsor has converted the text form from the previous labeling into tabular form. In the last paragraph [redacted] is added.

OVERDOSAGE:

The sponsor has changed the language of the recommended statements in this section, which needs to be reviewed by a MO. Also, the statement of medial lethal dose needs to be reviewed by a pharmacologist. (The statement starts with the oral median lethal dose and refers to the maximum recommended inhalation dose).

DOSAGE AND ADMINISTRATION:

The age group should be changed back to 12 years and above.

The last paragraph recommending "test spray" is added.

HOW SUPPLIED:

The reference to [redacted]-g size (institutional use) appeared first time in supplement S-020.

Patient's Instructions for Use:

Instruction number 7 from previous labeling is moved to number 2. The phrase "Avoid spraying in eyes." should be added.

Recommendation: Supplement S-023 will supersede pending labeling supplements S-017, S-019 and S-020; therefore, they will be acknowledged and retained. Supplement S-023 is approvable, provided sponsor agrees to make the changes listed above.

An action letter will be drafted, after all the reviews are completed.

/S/ 6-24-97

Parinda Jani
Project Manager

/S/ 6-18-97 CONCUR

Miriam Pina, M.D.
Clinical Reviewer

/S/ 6-24-97 CONCUR

Virgil Whitehurst, Ph.D.
Pharmacology Reviewer

/S/ 6.20.97 CONCUR

John Leak, Ph.D.
Chemistry Reviewer

CC:
NDA 17-559
DIV FILE/HFD-570
HFD-570/SCHUMAKER
HFD-570/PINA
HFD-570/LEAK
HFD-570/WHITEHURST
HFD-570/JANI/4-6-97

APPEARS THIS WAY
ON ORIGINAL

NOV - 4 1998

PROJECT MANAGER'S LABELING REVIEW

NDA: 17-559/S-023

Products: Proventil Inhalation Aerosol

Project Manager: Parinda Jani

Sponsor: Schering Corporation

Date submitted: December 23, 1996
September 24, 1998 (subject of this review)

Background: Supplement S-023 provides for the changes recommended by the Division for all beta-agonists. On June 24, 1997, an approvable letter was sent to the sponsor requesting additional information. On September 24, 1998, sponsor responded to the AE letter, which is the subject of this review.

DESCRIPTION:
In the first sentence of the third paragraph "pressurized" should be added before metered-dose. The dose delivered from the valve should be corrected to 100mcg.

CLINICAL PHARMACOLOGY:
The first sentence of the second paragraph should be revised to "*In vitro* studies and *in vivo* pharmacologic studies have demonstrated that albuterol, has a preferential effect on $beta_2$-adrenergic receptors compared with isoproterenol." The word [redacted] should be deleted from the second sentence. The last sentence should be revised to "The precise function of these receptors has not been established."

The first sentence of the third paragraph should be revised to "In controlled clinical trials, albuterol has been shown 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."

Preclinical:
In the first sentence of the first paragraph the words [redacted] should be changed to "amounting to."

The last sentence of the second paragraph should be revised to "The clinical significance of these finding is unknown."

Pharmacokinetics:
There are no changes made to this section.

Clinical Trials:
There are no changes made to this section.

INDICATION AND USAGE:
There are no changes made to this section.

CONTRAINDICATIONS:
The words "albuterol or" should be added after "hypersensitivity to."

WARNINGS:
The term "ECG" should be spelled out as "electrocardiogram."

PRECAUTIONS: General:
The last sentence of the first paragraph should be revised to "Clinically significant changes in systolic and diastolic blood pressure have been seen and could be expected to occur in some patients after use of any beta-adrenergic bronchodilator."

The second sentence of the second paragraph should be revised to "As with other beta-agonists, albuterol may produce....."

Information for Patients:
There are no changes made to this section.

Drug Interactions: The word "short-acting" should be added in the first sentence.

Drug Interactions: Monoamine Oxidase Inhibitors or Tricyclic Antidepressants:
The word "extreme" should be added before caution.

Carcinogenesis, Mutagenesis, and Impairment of Fertility, and Teratogenic Effects-Pregnancy Category C:
The sponsor was asked to include the following information in the labeling.

1. Names of the mutagenic cell types used for the mutagenicity assays

2. The doses, duration of study, species name, and the route of administration for the carcinogenicity study in hamsters; and

3. All doses used in carcinogenicity and reproduction studies.

The sponsor has not provided any information, but based on the information that the Agency has [redacted], this section should be updated. A review by a pharmacologist is needed.

Use in Labor and Delivery:
There are no changes made to this section.

Tocolysis:
The third sentence should be revised to "Serious adverse reactions, including maternal pulmonary edema, have been reported during or following treatment of premature labor with beta$_2$-agonists, including albuterol."

Nursing Mothers:
There are no changes made to this section.

Pediatric Use:
There are no changes made to this section.

ADVERSE REACTIONS:
The title of the table should be changed to "Percent Incidence of Adverse Reactions in Patients ≥ Years of Age". Each AE should be listed individually. (i.e., Tremor or Nausea, Dizziness or Heartburn). The statement [redacted] should be revised to "Cases of urticaria, angioedema, rash, bronchospasm, hoarseness, oropharyngeal edema, and arrhythmias (including atrial fibrillation, supraventricular tachycardia, extrasystoles) have been reported after the use of inhaled albuterol."

OVERDOSAGE:
The median lethal dose statement needs to be reviewed by a pharmacologist.

DOSAGE AND ADMINISTRATION:
The third paragraph should be revised to "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 patients and treatment regimen, giving special consideration to the possible need for anti-inflamamtory treatment, e.g., corticosteroids."

HOW SUPPLIED:
The dose delivery from the valve should be corrected to 100 mcg.

Patient's Instructions for Use:
The color of the mouthpiece [redacted] should be described in Item # 1.

The "Warnings" section should be revised to "The action of PROVENTIL Inhalation Aerosol may last up to 6 hours or longer. Proventil Inhalation Aerosol should not be used more frequently than recommended. Do not increase the dose or frequency of Proventil Inhalation Aerosol without consulting your physician. If you find that treatment with Proventil Inhalation Aerosol becomes less effective for symptomatic relief, your symptoms become worse, and/or you need to use the product more frequently than usual, you should seek immediate medical attention. While taking PROVENTIL Inhalation Aerosol, other asthma drugs and inhaled medicines should be used only as prescribed by your physician."

Recommendation: Supplement S-023 should be approved. Draft approval letter is attached.

/S/

Parinda Jani
Project Manager

10-2-98
Date

/S/

Badrul Chowdhury, M.D.
Clinical Reviewer

CONCUR

10/22/98
Date

/S/

Virgil Whitehurst, Ph.D.
Pharmacologist

CONCUR

10-14-98
Date

APPEARS THIS WAY
ON ORIGINAL

14 **Page(s) Redacted**

Draft

Labeling

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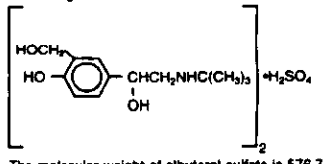
F-17543342 1261

PROVENTIL®
brand of albuterol sulfate, USP
REPETABS® brand of
extended-release Tablets
PROVENTIL®
brand of albuterol sulfate, USP
Tablets

DESCRIPTION PROVENTIL REPETABS Tablets and PROVENTIL Tablets contain albuterol sulfate, USP, the racemic form of albuterol and a relatively selective beta$_2$-adrenergic bronchodilator. Albuterol sulfate has the chemical name α^1-[(*tert*-Butylamino)methyl]-4-hydroxy-*m*-xylene-α, α'-diol sulfate (2:1) (salt), and the following chemical structure:



The molecular weight of albuterol sulfate is 576.7, and the empirical formula is $(C_{13}H_{21}NO_3)_2{\cdot}H_2SO_4$. Albuterol sulfate is a white crystalline powder, soluble in water and slightly soluble in ethanol. The World Health Organization recommended name for albuterol base is salbutamol.

Each PROVENTIL REPETABS Tablet for oral administration contains a total of 4 mg (2 mg in the coating for immediate release and 2 mg in the core for release after several hours) of albuterol as 4.8 mg of albuterol sulfate.

Each PROVENTIL Tablet for oral administration contains 2 or 4 mg of albuterol as 2.4 and 4.8 mg of albuterol sulfate, respectively.

The inactive ingredients for PROVENTIL REPETABS Tablets include: acacia, butylparaben, calcium phosphate, calcium sulfate, carnauba wax, corn starch, lactose, magnesium stearate, neutral soap, oleic acid, rosin, sugar, talc, titanium dioxide, white wax, and zein.

The inactive ingredients for PROVENTIL Tablets, 2 and 4 mg include: starch corn food grade, lactose monohydrate, NF; and magnesium stearate, NF.

CLINICAL PHARMACOLOGY The primary action of beta-adrenergic drugs, including albuterol, is to stimulate adenyl cyclase, the enzyme which catalyzes the formation of cyclic-3',5'-adenosine monophosphate (cyclic AMP) from adenosine triphosphate (ATP) in beta-adrenergic cells. The cyclic AMP thus formed mediates the cellular responses. Increased cyclic AMP levels are associated with relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

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 in 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.

In controlled clinical trials, albuterol has been shown 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 agonist drugs, can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, symptoms, and/or ECG changes.

Albuterol is longer acting than isoproterenol in most patients by any route of administration because it is not a substrate for the cellular uptake processes for catecholamines nor for catechol-*O*-methyl transferase.

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

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 beta-agonists

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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 beta-agonists and methylxanthines are administered concurrently. The clinical significance of these findings is unknown.

Pharmacokinetics: Albuterol is rapidly and well absorbed following oral administration.

In studies involving normal volunteers, the mean steady-state peak and trough plasma levels of albuterol were 6.7 and 3.8 ng/mL, respectively, following dosing with a 2 mg PROVENTIL Tablet every 6 hours and 14.8 and 8.6 ng/mL, respectively, following dosing with a 4 mg PROVENTIL Tablet every 6 hours. Maximum albuterol plasma levels are usually obtained between 2 and 3 hours after dosing, and the elimination half-life is 5 to 6 hours. These data indicate that albuterol administered orally is dose proportional and exhibits dose independent pharmacokinetics.

PROVENTIL REPETABS Tablets have been formulated to provide a duration of action of up to 12 hours. In studies conducted in normal volunteers, the mean steady-state peak and trough plasma levels of albuterol were 6.5 and 3.0 ng/mL, respectively, following dosing with a 4 mg PROVENTIL REPETABS Tablet every 12 hours. In addition, it has been shown that administration of a 4 mg PROVENTIL REPETABS Tablet every 12 hours, and a 2 mg PROVENTIL Tablet every 6 hours for 5 days gave comparable peak albuterol levels and similar extent of absorption at steady state.

In other studies, the analysis of urine samples of patients given tritiated albuterol (4 to 10 mg) orally showed that 65% to 90% of the dose was excreted over 3 days, with the majority of the dose being excreted within the first 24 hours. Sixty percent of this radioactivity was shown to be the metabolite. Feces collected over this period contained 4% of the administered dose.

Clinical Trials: In controlled clinical trials in patients with asthma, the onset of improvement in pulmonary function, as measured by maximal mid-expiratory flow rate, MMEF, was noted within 30 minutes after a dose of PROVENTIL Tablets with peak improvement occurring between 2 and 3 hours. In controlled clinical trials, in which measurements were conducted for 6 hours, significant clinical improvement in pulmonary function (defined as maintaining a 15% or more increase in FEV_1 and a 20% or more increase in MMEF over baseline values) was observed in 60% of patients at 4 hours and in 40% at 6 hours. In other single-dose, controlled clinical trials, clinically significant improvement was observed in at least 40% of the patients at 8 hours with the 4 mg PROVENTIL Tablet. No decrease in the effectiveness of PROVENTIL Tablets has been reported in patients who received long-term treatment with the drug in uncontrolled studies for periods up to 6 months.

In another controlled clinical study in asthmatic patients, it has been demonstrated that the initiation of therapy with either the 4 mg PROVENTIL REPETABS Tablet dosed every 12 hours, or the 2 mg PROVENTIL Tablet dosed every 6 hours, achieve therapeutically comparable effects.

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INDICATIONS AND USAGE PROVENTIL REPETABS Tablets and PROVENTIL Tablets are indicated for the relief of bronchospasm in adults and children 6 years of age and older with reversible obstructive airway disease.

CONTRAINDICATIONS PROVENTIL REPETABS Tablets and PROVENTIL Tablets are contraindicated in patients with a history of hypersensitivity to albuterol or any of their components.

WARNINGS **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 REPETABS Tablets and PROVENTIL Tablets than usual, this may be a marker of destabilization of asthma and requires re-evaluation of the patient and the treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment, eg, corticosteroids.

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.

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

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

Rarely, erythema multiforme and Stevens-Johnson syndrome have been associated with the administration of oral albuterol sulfate in children.

PRECAUTIONS **General:** Albuterol, 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, hyperthyroidism, 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 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 pre-existing diabetes mellitus and ketoacidosis. As with other beta-agonists, albuterol may produce significant hypokalemia in some patients, possibly through intracellular shunt-

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Large doses of intravenous albuterol have been reported to aggravate pre-existing 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: Patients being treated with PROVENTIL REPETABS Tablets or PROVENTIL Tablets should receive the following information and instructions. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

The action of PROVENTIL REPETABS Tablets may last up to 12 hours or longer, and the action of PROVENTIL Tablets may last up to 6 to 8 hours or longer. PROVENTIL REPETABS Tablets and PROVENTIL Tablets should not be taken more frequently than recommended. Do not increase the dose or frequency of PROVENTIL REPETABS Tablets or PROVENTIL Tablets without consulting your physician. If you find that treatment with PROVENTIL REPETABS Tablets or PROVENTIL Tablets becomes less effective for symptomatic relief, your symptoms become worse, and/or you need to take the product more frequently than usual, you should seek medical attention immediately. While you are taking PROVENTIL REPETABS Tablets or PROVENTIL Tablets, other inhaled drugs and asthma medications should be taken only as directed by your physician. Common adverse effects include palpitations, chest pain, rapid heart rate, tremor, or nervousness. If you are pregnant or nursing, contact your physician about the use of PROVENTIL REPETABS Tablets or PROVENTIL Tablets. Effective and safe use of PROVENTIL REPETABS Tablets or PROVENTIL Tablets includes an understanding of the way that it should be administered.

Drug Interactions: The concomitant use of PROVENTIL REPETABS Tablets or PROVENTIL Tablets and other oral sympathomimetic agents is not recommended since such combined use may lead to deleterious cardiovascular effects. This recommendation does not preclude the judicious use of an aerosol bronchodilator of the adrenergic stimulant type in patients receiving PROVENTIL REPETABS Tablets or PROVENTIL Tablets. Such concomitant use, however, should be individualized and not given on a routine basis. If regular coadministration is required, then alternative therapy should be considered.

Beta Blockers: Beta-adrenergic receptor blocking agents not only block the pulmonary effect of beta-agonists, such as PROVENTIL REPETABS Tablets or PROVENTIL Tablets 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 be considered, although they should be administered with caution.

Diuretics: The ECG changes and/or hypokalemia that 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.

Digoxin: Mean decreases of 16% to 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 this finding 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 concurrently receiving digoxin and albuterol.

Monoamine Oxidase Inhibitors or Tricyclic Antidepressants: Albuterol 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 vascular 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 and above dietary doses of 2 mg/kg (corresponding to less than the maximum recommended daily oral dose for adults and children, on an mg/m² basis). In another study this effect was blocked by the coadministration of propranolol, a nonselective 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 65 times the maximum recommended daily oral dose for adults on an mg/m² basis and approximately 50 times the maximum recommended daily oral dose for children on an mg/m² basis). In a 22-month study in the

tablets of PROVENTIL Tablets, other inhaled drugs and asthma medications should be taken only as directed by your physician. Common adverse effects include palpitations, chest pain, rapid heart rate, tremor, or nervousness. If you are pregnant or nursing, contact your physician about the use of PROVENTIL REPETABS Tablets or PROVENTIL Tablets. Effective and safe use of PROVENTIL REPETABS Tablets or PROVENTIL Tablets includes an understanding of the way that it should be administered.

Drug Interactions: The concomitant use of PROVENTIL REPETABS Tablets or PROVENTIL Tablets and other oral sympathomimetic agents is not recommended since such combined use may lead to deleterious cardiovascular effects. This recommendation does not preclude the judicious use of an aerosol bronchodilator of the adrenergic stimulant type in patients receiving PROVENTIL REPETABS Tablets or PROVENTIL Tablets. Such concomitant use, however, should be individualized and not given on a routine basis. If regular coadministration is required, then alternative therapy should be considered.

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Diuretics: The ECG changes and/or hypokalemia that 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.

Digoxin: Mean decreases of 16% to 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 this finding 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 concurrently receiving digoxin and albuterol.

Monoamine Oxidase Inhibitors or Tricyclic Antidepressants: Albuterol 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 vascular 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 and above dietary doses of 2 mg/kg (corresponding to less than the maximum recommended daily oral dose for adults and children, on an mg/m^2 basis). In another study this effect was blocked by the coadministration of propranolol, a nonselective 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 65 times the maximum recommended daily oral dose for adults on an mg/m^2 basis and approximately 50 times the maximum recommended daily oral dose for children on an 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 8 times the maximum recommended daily oral dose for adults and children on an 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.

Reproduction studies in rats demonstrated no evidence of impaired fertility at oral doses of albuterol sulfate up to 50 mg/kg (approximately 15 times the maximum recommended daily oral dose for adults on an 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 (sc) doses at and above 0.25 mg/kg (corresponding to less than the maximum recommended daily oral dose for adults on an mg/m^2 basis), induced cleft palate formation in 5 of 111 (4.5%) fetuses. At an sc dose of 2.5 mg/kg (corresponding to less than the maximum recommended daily oral dose for adults on an mg/m^2 basis) albuterol sulfate induced cleft palate formation in 10 of 108 (9.3%) fetuses. The drug did not induce cleft palate formation when administered at an sc dose of 0.025 mg/kg (significantly less than the maximum recommended daily oral dose for adults on an 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.

A reproduction study in Stride Dutch rabbits revealed cranioschisis in 7 of 19 (37%) fetuses when albuterol was administered orally at a dose of 50 mg/kg (approximately 25 times the maximum recommended daily oral dose for adults on an mg/m^2 basis).

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

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, albuterol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

During worldwide marketing experience, 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 has not been established.

Labor and Delivery — Use in Labor: Because of the potential for beta-agonist interference with uterine contractility, use of PROVENTIL REPETABS Tablets or PROVENTIL Tablets 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 preterm labor. The benefit:risk ratio when albuterol is administered for tocolysis has not been established. Serious adverse reactions, including maternal pulmonary edema, have been reported during or following treatment of premature labor with beta$_2$-agonists, including albuterol.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because of the potential for tumorigenicity shown for albuterol in some animal studies, 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.

Pediatric Use: The safety and effectiveness of PROVENTIL Tablets and PROVENTIL REPETABS Tablets have been established in pediatric patients 6 years of age and older. Use of PROVENTIL REPETABS Tablets in these age groups is supported by evidence from adequate and well-controlled studies of PROVENTIL REPETABS Tablets in adults; the likelihood that the disease course, pathophysiology, and the drug's effect in pediatric and adult patients are substantially similar; the established safety and effectiveness of PROVENTIL Tablets in pediatric patients 6 years of age and older; and one clinical trial that provides evidence of the safety of PROVENTIL REPETABS Tablets in pediatric patients aged 6 to 12 years. The recommended dose of PROVENTIL REPETABS Tablets in the pediatric population is based upon the recommended pediatric dosing of PROVENTIL Tablets and pharmacokinetic studies in adults showing PROVENTIL REPETABS Tablets to have similar peak albuterol levels (ie, C_{max}) and exposures (ie, AUC) as PROVENTIL Tablets administered every 6 hours at one-half of the PROVENTIL REPETABS Tablets dose.

Safety and effectiveness in pediatric patients below the age of 6 years for PROVENTIL REPETABS Tablets and PROVENTIL Tablets have not been established.

ADVERSE REACTIONS The adverse reactions to albuterol are similar in nature to those of other sympathomimetic agents.

PROVENTIL Tablets
Adverse Experience Incidences (% of patients) in Adults and Children 6 Years of Age and Older

Adverse Event	Percent Incidence
Central Nervous System	
Nervousness	20
Tremor	20
Headache	7
Dizziness	2
Weakness	2
Sleeplessness	2
Irritability	<1
Drowsiness	<1
Restlessness	<1
Cardiovascular	
Palpitations	5
Tachycardia	5
Flushing	<1
Chest discomfort	<1
Musculoskeletal	
Muscle cramps	3
Gastrointestinal	
Nausea	2
Genitourinary	
Difficulty in micturition	<1

PROVENTIL REPETABS Tablets
Incidence of Adverse Reactions (% of Patients) in a 1-Week Clinical Trial*

Adverse Event	PROVENTIL REPETABS Tablets (4 mg every 12 hours)	PROVENTIL Tablets (2 mg every 6 hours)
Nausea	4	4
Nervousness	2	6
Vomiting	2	4
Somnolence	2	2

*This table includes adverse reactions considered to

Incidence of Adverse Reactions (% of Patients) in a 1-Week Clinical Trial*

Adverse Event	PROVENTIL REPETABS Tablets (4 mg every 12 hours)	PROVENTIL Tablets (2 mg every 6 hours)
Nausea	4	4
Nervousness	2	6
Vomiting	2	4
Somnolence	2	2

*This table includes adverse reactions considered to be possibly or probably treatment related, in a 1-week clinical trial comparing a 4 mg PROVENTIL REPETABS Tablet administered every 12 hours to a 2 mg PROVENTIL Tablet administered every 6 hours.

Although not reported for PROVENTIL REPETABS Tablets in the above study, there have been reports of tremor in other trials. When all clinical experience is considered, the incidence of tremor is approximately the same as that seen with PROVENTIL Tablets.

A placebo-controlled trial of 4 weeks duration in 157 mild-to-moderate asthmatic children aged 6 to 12 years, demonstrated the safety of escalating doses of PROVENTIL REPETABS Tablets. In this study, the starting dose of PROVENTIL REPETABS Tablets was 4 mg twice daily. Patients were advanced to a maximum of 12 mg PROVENTIL REPETABS Tablets twice daily by the investigator, based on patient tolerance and response. Only one of the 79 children treated with PROVENTIL REPETABS Tablets was advanced to the maximum daily dose of 12 mg twice daily. The following treatment-related adverse events occurred in more than 5% of treated patients and were greater in PROVENTIL REPETABS Tablets patients when compared to placebo:

Incidence of Adverse Events (% of Patients) in a 4-Week Placebo-Controlled Trial in 157 Children 6-12 Years of Age

Adverse Event	PROVENTIL REPETABS Tablets %	Placebo %
Headache	22	9
Nervousness	13	6
Insomnia	11	5
Tremor	10	1
Palpitation	8	1
Tachycardia	8	1

Other adverse events were noted in 5% or fewer patients, or had equal or greater rates of occurrence in placebo patients than in PROVENTIL REPETABS Tablets patients.

Cases of urticaria, angioedema, rash, bronchospasm, oropharyngeal edema, and arrhythmias (including atrial fibrillation, supraventricular tachycardia, and extrasystoles) have been reported after the use of PROVENTIL Tablets and PROVENTIL REPETABS Tablets.

In addition to those adverse reactions reported above, albuterol, like other sympathomimetic agents, can cause adverse reactions such as angina, central nervous system stimulation, drying or irritation of the oropharynx, hypertension, unusual taste, and vertigo.

The reactions are generally transient in nature, and it is usually not necessary to discontinue treatment with PROVENTIL REPETABS Tablets or PROVENTIL Tablets. In selected cases, however, dosage may be reduced temporarily; after the reaction has subsided, dosage should be increased in small increments to the optimal dosage.

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, angina, hypertension, tachycardia with rates up to 200 beats per minute, nervousness, headache, tremor, dry mouth, palpitation, nausea, dizziness, and insomnia. In addition, seizures, hypotension, arrhythmias, fatigue, malaise, and hypokalemia may also occur. As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of PROVENTIL REPETABS Tablets and PROVENTIL Tablets. Treatment consists of discontinuation of PROVENTIL REPETABS Tablets and PROVENTIL Tablets 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 REPETABS Tablets or PROVENTIL Tablets.

The oral median lethal dose of albuterol sulfate in mice is greater than 2000 mg/kg (approximately 250 times the maximum recommended daily oral dose for adults on an mg/m² basis and approximately 200 times the maximum recommended daily oral dose for children on an mg/m² basis). In mature rats, the subcutaneous (sc) median lethal dose of albuterol sulfate is approximately 450 mg/kg (approximately 110 times the maximum recommended daily oral dose for adults on an mg/m² basis, and approximately 90 times the maximum recommended daily oral dose for children on an mg/m² basis). In small young rats, the subcutaneous median lethal dose is approximately 2000 mg/kg (approximately 510 times the maximum recommended daily oral dose for adults on an mg/m² basis, and approximately 400 times the maximum recommended daily oral dose for children on an mg/m² basis).

DOSAGE AND ADMINISTRATION The following dosages of PROVENTIL REPETABS Tablets and PROVENTIL Tablets are expressed in terms of albuterol base.

PROVENTIL REPETABS Tablets

Usual Dose: **Pediatric Patients 6 to 12 years of age:** For pediatric patients 6 to 12 years of age, the usual starting dosage of PROVENTIL REPETABS Tablets is 4 mg (one tablet) every 12 hours.

Adults and Pediatric Patients over 12 years of age: *For adults and children over 12 years of age,* the usual starting dosage of PROVENTIL REPETABS Tablets is 4 or 8 mg (one or two tablets) every 12

DOSAGE AND ADMINISTRATION The following dosages of PROVENTIL REPETABS Tablets and PROVENTIL Tablets are expressed in terms of albuterol base.

PROVENTIL REPETABS Tablets

Usual Dose: **Pediatric Patients 6 to 12 years of age:** For pediatric patients 6 to 12 years of age, the usual starting dosage of PROVENTIL REPETABS Tablets is 4 mg (one tablet) every 12 hours.

Adults and Pediatric Patients over 12 years of age: For adults and children over 12 years of age, the usual starting dosage of PROVENTIL REPETABS Tablets is 4 or 8 mg (one or two tablets) every 12 hours.

Dosage Adjustment in Pediatric Patients 6 to 12 years of age: Dosages of PROVENTIL REPETABS Tablets above 4 mg twice a day should be used only when the patient fails to respond to this dosage while on otherwise optimized asthma therapy. In such instances, the PROVENTIL REPETABS Tablets dosage may be increased cautiously stepwise as tolerated if a favorable response does not occur with the 4 mg twice daily initial dosage. The maximum recommended dosage of PROVENTIL REPETABS Tablets in pediatric patients aged 6 to 11 years is 12 mg twice a day.

Dosage Adjustment in Adults and Pediatric Patients over 12 years of age: Dosages of PROVENTIL REPETABS Tablets above 8 mg twice a day should be used only when the patient fails to respond to this dosage while on otherwise optimized asthma therapy. The PROVENTIL REPETABS Tablets dosage may be increased cautiously stepwise as tolerated if a favorable response does not occur with the 8 mg twice daily dosage. The maximum recommended dosage of PROVENTIL REPETABS Tablets in adults and pediatric patients over 12 years of age is 16 mg twice a day.

The total daily dose should not exceed 32 mg per day in adults and children over 12 years of age.

Switching to PROVENTIL REPETABS Tablets: Patients currently maintained on PROVENTIL Tablets can be switched to PROVENTIL REPETABS Tablets. For example, the administration of a 4 mg PROVENTIL REPETABS Tablet every 12 hours is clinically comparable to one 2 mg PROVENTIL Tablet every 6 hours. Multiples of this regimen up to the maximum recommended daily dose also apply.

PROVENTIL Tablets

Usual Dose: **Pediatric Patients 6 to 12 years of age:** For pediatric patients 6 to 12 years of age, the usual starting dosage is 2 mg three or four times a day.

Adults and Pediatric Patients over 12 years of age: For adults and pediatric patients over 12 years of age, the usual starting dosage is 2 mg or 4 mg three or four times a day.

Dosage Adjustment: **Pediatric Patients 6 to 12 years of age who fail to respond to the initial starting dosage of 2 mg four times a day:** For pediatric patients from 6 to 12 years of age who fail to respond to the initial starting dosage of 2 mg four times a day, the dosage may be cautiously increased stepwise, but not to exceed 24 mg per day (given in divided doses).

Adults and Pediatric Patients over 12 years of age: For adults and pedicatric patients over 12 years of age. A dosage above 4 mg four times a day should be used only when the patient fails to respond to lower doses. The dosage should be increased cautiously stepwise up to a maximum of 8 mg four times a day as tolerated if a favorable response does not occur with the 4 mg initial dosage.

Elderly Patients and Those Sensitive to Beta-Adrenergic Stimulators: An initial dosage of 2 mg three or four times a day is recommended for elderly patients and for those with a history of unusual sensitivity to beta-adrenergic stimulators. If adequate bronchodilation is not obtained, dosage may be increased gradually as tolerated to as much as 8 mg three or four times a day.

The total daily dose should not exceed 24 mg per day in pediatric patients from 6 to 12 years of age, and 32 mg per day in adults and pediatric patients over 12 years of age.

HOW SUPPLIED PROVENTIL REPETABS Tablets, 4 mg albuterol as the sulfate (2 mg in the coating for immediate release and 2 mg in the core for release after several hours), white, round, coated tablets, branded in red on one side with the Schering trademark, and product identification numbers, 431, high-density polyethylene bottles of 100 (NDC 0085-0431-02) and 500 (NDC 0085-0431-03) and boxes of 100 for unit-dose dispensing (NDC 0085-0431-04).

PROVENTIL Tablets, 2 mg albuterol as the sulfate, white to off-white, round, flat, beveled-edge tablet, scored diametrically on one side and engraved with digits 252 on each side of the score with the product name (PROVENTIL) and the number 2 on the other side, high-density polyethylene bottles of 100 (NDC 0085-0252-02) and 500 (NDC 0085-0252-03).

PROVENTIL Tablets, 4 mg albuterol as the sulfate, white to off-white, round, flat, beveled-edge tablet, scored diametrically on one side and engraved with digits 573 on each side of the score with the product name (PROVENTIL) and the number 4 on the other side, high density polyethylene bottles of 100 (NDC 0085-0573-02) and 500 (NDC 0085-0573-03).

Store PROVENTIL REPETABS Tablets between 2° and 25°C (36° and 77°F), and PROVENTIL Tablets between 2° and 30°C (36° and 86°F). Protect

PROVENTIL Tablets are expressed in terms of albuterol base.

PROVENTIL REPETABS Tablets

Usual Dose: **Pediatric Patients 6 to 12 years of age:** For pediatric patients 6 to 12 years of age, the usual starting dosage of PROVENTIL REPETABS Tablets is 4 mg (one tablet) every 12 hours.

Adults and Pediatric Patients over 12 years of age: For adults and children over 12 years of age, the usual starting dosage of PROVENTIL REPETABS Tablets is 4 or 8 mg (one or two tablets) every 12 hours.

Dosage Adjustment in Pediatric Patients 6 to 12 years of age: Dosages of PROVENTIL REPETABS Tablets above 4 mg twice a day should be used only when the patient fails to respond to this dosage while on otherwise optimized asthma therapy. In such instances, the PROVENTIL REPETABS Tablets dosage may be increased cautiously stepwise as tolerated if a favorable response does not occur with the 4 mg twice daily initial dosage. The maximum recommended dosage of PROVENTIL REPETABS Tablets in pediatric patients aged 6 to 11 years is 12 mg twice a day.

Dosage Adjustment in Adults and Pediatric Patients over 12 years of age: Dosages of PROVENTIL REPETABS Tablets above 8 mg twice a day should be used only when the patient fails to respond to this dosage while on otherwise optimized asthma therapy. The PROVENTIL REPETABS Tablets dosage may be increased cautiously stepwise as tolerated if a favorable response does not occur with the 8 mg twice daily dosage. The maximum recommended dosage of PROVENTIL REPETABS Tablets in adults and pediatric patients over 12 years of age is 16 mg twice a day.

The total daily dose should not exceed 32 mg per day in adults and children over 12 years of age.

Switching to PROVENTIL REPETABS Tablets: Patients currently maintained on PROVENTIL Tablets can be switched to PROVENTIL REPETABS Tablets. For example, the administration of a 4 mg PROVENTIL REPETABS Tablet every 12 hours is clinically comparable to one 2 mg PROVENTIL Tablet every 6 hours. Multiples of this regimen up to the maximum recommended daily dose also apply.

PROVENTIL Tablets

Usual Dose: **Pediatric Patients 6 to 12 years of age:** For pediatric patients 6 to 12 years of age, the usual starting dosage is 2 mg three or four times a day.

Adults and Pediatric Patients over 12 years of age: For adults and pediatric patients over 12 years of age, the usual starting dosage is 2 mg or 4 mg three or four times a day.

Dosage Adjustment: **Pediatric Patients 6 to 12 years of age who fail to respond to the initial starting dosage of 2 mg four times a day:** For pediatric patients from 6 to 12 years of age who fail to respond to the initial starting dosage of 2 mg four times a day, the dosage may be cautiously increased stepwise, but not to exceed 24 mg per day (given in divided doses).

Adults and Pediatric Patients over 12 years of age: For adults and pedicatric patients over 12 years of age. A dosage above 4 mg four times a day should be used only when the patient fails to respond to lower doses. The dosage should be increased cautiously stepwise up to a maximum of 8 mg four times a day as tolerated if a favorable response does not occur with the 4 mg initial dosage.

Elderly Patients and Those Sensitive to Beta-Adrenergic Stimulators: An initial dosage of 2 mg three or four times a day is recommended for elderly patients and for those with a history of unusual sensitivity to beta-adrenergic stimulators. If adequate bronchodilation is not obtained, dosage may be increased gradually as tolerated to as much as 8 mg three or four times a day.

The total daily dose should not exceed 24 mg per day in pediatric patients from 6 to 12 years of age, and 32 mg per day in adults and pediatric patients over 12 years of age.

HOW SUPPLIED PROVENTIL REPETABS Tablets, 4 mg albuterol as the sulfate (2 mg in the coating for immediate release and 2 mg in the core for release after several hours), white, round, coated tablets, branded in red on one side with the Schering trademark, and product identification numbers, 431, high-density polyethylene bottles of 100 (NDC 0085-0431-02) and 500 (NDC 0085-0431-03) and boxes of 100 for unit-dose dispensing (NDC 0085-0431-04).

PROVENTIL Tablets, 2 mg albuterol as the sulfate, white to off-white, round, flat, beveled-edge tablet, scored diametrically on one side and engraved with digits 252 on each side of the score with the product name (PROVENTIL) and the number 2 on the other side, high-density polyethylene bottles of 100 (NDC 0085-0252-02) and 500 (NDC 0085-0252-03).

PROVENTIL Tablets, 4 mg albuterol as the sulfate, white to off-white, round, flat, beveled-edge tablet, scored diametrically on one side and engraved with digits 573 on each side of the score with the product name (PROVENTIL) and the number 4 on the other side, high-density polyethylene bottles of 100 (NDC 0085-0573-02) and 500 (NDC 0085-0573-03).

Store PROVENTIL REPETABS Tablets between 2° and 25°C (36° and 77°F), and PROVENTIL Tablets between 2° and 30°C (36° and 86°F). Protect PROVENTIL REPETABS Tablets in the unit-dose box from excessive moisture.

Schering Corporation
Kenilworth, NJ 07033 USA

Rev. 10/97 R-17543342

OCT - 5 1998

PROJECT MANAGER'S LABELING REVIEW

NDA: 17-853/S-016 and [redacted]

Project Manager: Parinda Jani

APPEARS THIS WAY
ON ORIGINAL

Sponsor: Schering Corporation

Products: Proventil Tablets and Proventil Repetabs Tablets

Date submitted: December 23, 1996
September 24, 1998 (subject of this review)

Background: These supplements provide for the changes recommended by the Division for all beta-agonists. On June 24, 1997, approvable letters were sent to the sponsor requesting additional information. Also, on September 18, 1997, Proventil Repetabs Tablets were approved for use in children 6 to 12 years of age (NDA 19-383/ S-011). On September 24, 1998, sponsor responded to the AE letters and has incorporated the changes recommended in the labeling approved for Proventil Repetabs, which is the subject of this review.

DESCRIPTION:
The sponsor has incorporated the recommended changes.

CLINICAL PHARMACOLOGY:
The first sentence of the second paragraph should be revised to "*In vitro* studies and *in vivo* pharmacologic studies have demonstrated that albuterol, has a preferential effect on beta$_2$-adrenergic receptors compared with isoproterenol." The word [redacted] should be deleted from the second sentence. The last sentence should be revised to "The precise function of these receptors has not been established."

The third paragraph should be revised to "In controlled clinical trials, albuterol has been shown 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."

Preclinical:
In the first sentence of the first paragraph the words [redacted] should be changed to "amounting to."

The paragraph "Studies in laboratory animals.....is unknown." was deleted by error and should be reinstated.

Pharmacokinetics:
There are no changes made to this section.

Clinical Trials:
There are no changes made to this section.

INDICATION AND USAGE:
There are no changes made to this section

CONTRAINDICATIONS:
The words "albuterol or" should be added after "hypersensitivity to."

WARNINGS:
The term "ECG" should be spelled out as "electrocardiogram."

PRECAUTIONS: General:
The last sentence of the first paragraph should be revised to "Clinically significant changes in systolic and diastolic blood pressure have been seen and could be expected to occur in some patients after use of any beta-adrenergic bronchodilator."

The second sentence of the second paragraph should be revised to "As with other beta-agonists, albuterol may produce....."

Information for Patients:
In the first sentence of the first paragraph should be replace with "may". The words should be replaced with "taken, take and taking."

Drug Interactions: Monoamine Oxidase Inhibitors or Tricyclic Antidepressants:
The word "extreme" should be added before caution.

Carcinogenesis, Mutagenesis, and Impairment of Fertility, and Teratogenic Effects-Pregnancy Category C:

The sponsor was asked to include the following information in the labeling.

1. Names of the mutagenic cell types used for the mutagenicity assays

2. The doses, duration of study, species name, and the route of administration for the carcinogenicity study in hamsters; and

3. All doses used in carcinogenicity and reproduction studies.

The sponsor has not provided any information, but based on the information that the Agency has this section should be updated. A review by a pharmacologist is needed.

Use in Labor and Delivery:
There are no changes made to this section.

Tocolysis:
The third sentence should be revised to "Serious adverse reactions, including maternal pulmonary edema, have been reported during or following treatment of premature labor with beta$_2$-agonists, including albuterol."

Nursing Mothers:
There are no changes made to this section.

Pediatric Use:
Changes approved in supplement S-011 (Proventil Repetabs Tablets) are incorporated in this section.

ADVERSE REACTIONS:
The paragraph "Although not reported for PROVENTIL REPETABS Tablets in the above study, there have been reports of tremor in other trials. When all clinical experience is considered, the incidence of tremor is approximately the same as that seen with PROVENTIL Tablets." should be moved before the adverse incidents in pediatric patients paragraph. The pediatric adverse events should be described in a tabular format. This section should be reviewed by a medical officer.

The statement "Cases of urticaria, angioedema, rash, bronchospasm, oropharyngeal edema, and arrhythmias (including atrial fibrillation, supraventricular tachycardia, extrasystoles) have been reported after the use of Proventil Repetabs Tablets and Proventil Tablets." should be added.

OVERDOSAGE:
The median lethal dose statement needs to be reviewed by a pharmacologist.

DOSAGE AND ADMINISTRATION:
There are no changes made to this section.

The recommended dosing age groups should be changed to: Adults and children over 12 years of age and children [redacted] 6 to 12 years of age.

HOW SUPPLIED:
The sponsor has included the type of bottles as recommended by the Division. The sponsor has added "beveled edge tablet, scored diametrically on one side and engraved with digits 252 on each side of the score with the product name (Proventil) and the number 2 on the other side" to the description of the Proventil Tablets.

Recommendation: Supplements S-016 (NDA 17-853) and S-010 (NDA 19-383) should be approved. Draft approval letter is attached.

/S/

Parinda Jani
Project Manager

10-5-98
Date

/S/

Badrul Chowdhury, M.D.
Clinical Reviewer

CONCUR

11/13/98
Date

/S/

Virgil Whitehurst, Ph.D.
Pharmacologist

CONCUR

10-12-98
Date

CC:
ORIG NDA/[redacted] 17-853 (S1) 19383
DIVE FILE/HFD-570 (2)
HFD-570/JANI/
HFD-570/SCHUMAKER /S/
HFD-570/CHOWDHURY
HFD-570/LEAK (S1) 11/4/98 10-5-98
HFD-570/WHITEHURST

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 17-559/S023
19-383/S010
17-853/S016

MEDICAL REVIEW(S)

JUN 13 1997

MEDICAL OFFICER REVIEW

Division of Pulmonary Drug Products (HFD-570)

APPLICATION #:	NDA 17-559/S-023	APPLICATION TYPE:	NDA labeling supplement
CATEGORY OF DRUG:	Short-acting beta agonist	PRODUCT/PROPRIETARY NAME:	Proventil inhalation Aerosol
SPONSOR:	Schering Corp.	USAN / Established Name:	Albuterol
		ROUTE OF ADMINISTRATION:	Inhaled
MEDICAL REVIEWER:	L. Miriam Pina, M.D.	REVIEW DATE:	June 13, 1997

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
01/03/97	01/06/97	Beta-Agonist Class Labeling supplement	

RELATED APPLICATIONS (if applicable)

Document Date:	APPLICATION Type:	Comments:
12/23/96 & 01/03/97	NDA 18-473	Ventolin MDI - Beta-Agonist Class Labeling supplement

Overview of Application/Review:

Supplement 023 provides for the changes recommended by the Division under Beta-Agonist Class labeling. This supplement supersedes pending labeling supplements S-0017, S-0019 and S-0020. The sponsor has followed most of the recommended changes in the labeling requested by the Division, but some changes are still needed.

Indication: Asthma

Patient population studied: Adult and pediatric

Outstanding Issues:

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: 6/13/97

Medical Team Leader: /S/ Date: 6/18/97

MEDICAL REVIEW

NDA#	17-559
MEDICAL REVIEWER:	Liza M. Pina, M.D.
PRODUCT:	Proventil Inhalation Aerosol
INDICATION:	Asthma
SPONSOR:	Schering Corp.

DOCUMENT REVIEWED:	Supplement 023
DATE SUBMITTED:	01/03/97
DATE REVIEW COMPLETED:	June 13, 1997

I. RÉSUMÉ

Supplement 023 provides for the changes recommended by the Division under Beta-Agonist Class labeling. This supplement supersedes pending labeling supplements S-017, S-019 and S-020. The sponsor has followed most of the recommended changes in the labeling requested by the Division, but some more changes are recommended.

II. BACKGROUND

In 1996 the Division issued a summary of recommendations for to update and harmonize the information provided in the labelings for this class of drugs. Sponsors were asked to make the recommended changes as applicable to their drug products.

III. REVIEW OF SUBMITTED LABELING SUPPLEMENT

This supplement was submitted in response to the Division's requests under the Beta-Agonist Class labeling. It was reviewed based on the last approved labeling supplement on file for this NDA, S-010, approved on April 22, 1986. The following recommendations pertain to the clinical information provided in the proposed labeling:

1. **Clinical Pharmacology section:**

First paragraph: It is acceptable. This paragraph appears in the approved label for [redacted]% aerosol solution.

Second paragraph: The phrase[redacted]

Third paragraph: The addition of this paragraph "In controlled clinical trials... EKG changes." has been approved in the labeling for the [redacted]% inhaled solution; it is acceptable.

Fifth paragraph: "The effects of rising... was also seen" is acceptable.

Pharmacokinetics: All the information regarding [redacted] may be confusing to the reader. This information should be deleted.

The paragraph: "Because of its gradual ... 44% as metabolite" has been deleted by the sponsor, but it provides important pharmacokinetic information and should be added under this subheading.

Clinical trials: The changes proposed by the sponsor under this subheading are acceptable.

2. **Indication and Usage section:**
In this section, under 21 CFR 201.57(c)(3)(I) can include the age group for which the product has shown evidence of effectiveness and safety. However, the sponsor's proposal to change the age indicated has not been justified, therefore, the label should state that this product is indicated to patients 12 years and above.

3. **Warning section:**
The content of the paragraph has been already addressed in other subheadings within this section. To avoid redundancy this paragraph should be deleted.

All other changes in this section are acceptable.

4. **Precautions:**
Some changes in wording are suggested for consistency with other albuterol products. See proposed labeling.

Pediatric Use: This subheading should state that this product

5. **Adverse reactions section:**
The Division requested that the adverse events be listed in a tabular format. Some changes in the format are suggested to the sponsor's proposed table. See proposed labeling.

The information regarding adverse events submitted by the sponsor in a As a result, these data should be deleted from the present labeling.

6. **Overdosage:**
The changes in the wording of this section are acceptable. The information on the median lethal dose will be reviewed by the pharmacology reviewer.

7. **Dosage and Administration:**
The information should be limited to patients 12 years of age and older

IV RECOMMENDATIONS

This supplement is approvable from the clinical point of view. Some changes are recommended for consistency of the information provided for other albuterol products.

V COMMENTS TO THE SPONSOR

1. Regarding **Clinical Pharmacology section:**

First paragraph: It is acceptable. This paragraph appears in the approved label for % aerosol solution.

Second paragraph: The phrase

Third paragraph: The addition of this paragraph: "In controlled clinical trials... EKG changes" has been approved in the labeling for the % inhaled solution; it is acceptable.

Fifth paragraph: "The effects of rising... was also seen" is acceptable.

Pharmacokinetics: All the information regarding [redacted] may be confusing to the reader. This information should be deleted.

The paragraph: "Because of its gradual ... 44% as metabolite" has been deleted by the sponsor, but it provides important pharmacokinetic information and should be added under this subheading.

Clinical trials: The changes proposed by the sponsor under this subheading are acceptable.

2. **Indication and Usage section:**
This section, under 21 CFR 201.57(c)(3)(I), can include the age group for which the product has shown evidence of effectiveness and safety. However, the sponsor's proposal to change the age indicated [redacted] has not been justified, therefore, the label should state that this product is indicated to [redacted] patients 12 years and above.

3. **Warning section:**
The content of the paragraph [redacted] has been already addressed in other subheadings within this section. To avoid redundancy this paragraph should be deleted.

All other changes in this section are acceptable.

4. **Precautions:**
Some changes in wording are suggested for consistency with other albuterol products. See proposed labeling.

Pediatric Use: This subheading should state that safety and efficacy of this product in children below the age of 12 years have not been established.

5. **Adverse reactions section:**
The Division requested that the adverse events be listed in a tabular format. Some changes in the format of the sponsor's proposed table are suggested. See proposed labeling.

The information regarding adverse events [redacted] As a result, these data should be deleted from the present labeling.

6. **Overdosage:**
The changes in the wording of this section are acceptable. The information on the median lethal dose will be reviewed by the pharmacology reviewer.

7. **Dosage and Administration:**
The information should be limited to patients 12 years of age and older [redacted]

/S/
Liza M. Pina, M.D.
Medical Reviewer
June 13, 1997

cc:
NDA
HFD-750 /division file
/Pina
/Himmel
/Jani

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 17-559/S023
19-383/S010
17-853/S016

CHEMISTRY REVIEW(S)

JUN 24 1997

CHEMIST'S REVIEW

1. ORGANIZATION HFD-570 DPDP		2. NDA NUMBER 17-559	
3. NAME AND ADDRESS OF APPLICANT *(City and State)* Schering Corporation 2000 Galloping Hill Road Kenilworth, NJ 07033		4. AF NUMBER	
		5. SUPPLEMENT (S) NUMBER(S)	DATES(S)
6. NAME OF DRUG Proventil Inhalation Aerosol	7. NONPROPRIETARY NAME albuterol metered dose aerosol	SLR-023	12/27/96
8. SUPPLEMENT PROVIDES FOR: changes recommended by the division under Beta-agonist Class labeling.		9. AMENDMENTS DATES	
10. PHARMACOLOGICAL CATEGORY $Beta_2$-adrenergic bronchodilator	11. HOW DISPENSED RX X OTC _____	12. RELATED IND/NDA/DMF	
13. DOSAGE FORM(S) Metered Dose Aerosol	14. POTENCY 90μg/burst		
15. CHEMICAL NAME AND STRUCTURE		16. RECORDS AND REPORTS CURRENT YES_____ NO_____ REVIEWED YES_____ NO_____	

17. COMMENTS
This is an evaluation of the DESCRIPTION and HOW SUPPLIED sections of the proposed clean copy of the labeling. Adequacy will be based on 21CFR 201.57 and 201.100 parts of the regulations.

doc # 17559S23.SUP

18. CONCLUSIONS AND RECOMMENDATIONS
The project manager has indicated in her review that the phrase "Avoid spraying in eyes" should be added to the patient's instruction for use.

With this change, the supplement is approvable from a chemistry and manufacturing standpoint.

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
John C. Leak, Ph.D.	/S/	6/20/97

DISTRIBUTION ORIGINAL JACKET ___ DIVISION FILE ___ REVIEWER ___ CSO ___ SUP. CHEMIST ___

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 17-559/S023
19-383/S010
17-853/S016

PHARMACOLOGY REVIEW(S)

JUN 24 1997

Division of Pulmonary Drug Products

Review of Pharmacology and Toxicology Data

Reviewer : VEWhitehurst

Date Reviewed : June 23, 1997

NDAs : NDA 17559/S-017, S-019, S-020 and S-023

Submission Dates : January 3, 1989/S-017
June 1, 1989/S-017
November 9, 1993/S-019
November 19, 1989/S-019
February 25, 1994/S-019
April 14, 1995/S-020
December 23, 1996/S-023
January 3, 1997/S-023

Sponsor : Schering Corp.

Drug : Proventil Inhalation Aerosol (albuterol sulfate)

Category : beta agonist

Indication : Treatment of asthma

Reason for the review : Class labeling review for Proventil Inhalational Aerosol (albuterol sulfate).

Dose : Adults and children, 12 years and older : Maximum daily dose is 6 inhalations (90 µg/ inhalation) or 540 µg daily, approximately 11 µg/kg for a 50 kg person.

Route of administration : oral

Reason for the supplement : Class labeling for Proventil Inhalation Aerosol.

3 **Page(s) Redacted**

Draft

Labeling

19383

1

OCT 19 1998

Division of Pulmonary Drug Products

Review of Pharmacology/Toxicology Data

Review: Final Labeling

Reviewer: VEWhitehurst

Date of submission: 9/24/98-SLR 016 (NDA 17,853)
SLR 010 (NDA 19,383)

Review completion date: October 19, 1998

Information to be conveyed to the sponsor: yes

HFD; HFD 570

NDA: NDA 17,853 and NDA 19,383

Sponsor: Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033-0530

Drug: Proventil Repetab Tablets (19, 383) and Proventil Tablets (17,853)

Category: Beta Adrenergic agonist

Indication: Treatment or prevention of acute bronchospasmin patents years of age and older with obstructive airway disease and attacks of bronchospasms.

Administration: Oral

Dosage: Children: 6 –12 years, maximun daily dose, 24 mg or 1.2 mg/kg for a 6 year old year old weighting 20 kg.
Adult : Adults, maximun .daily dose. 32 mg or 0.64 mg /kg for a 50 kg adults.

Labeling for Proventil Repetabs Tablets and Proventil Tablets:

The preclinical sections should be revised as following:

Preclinical section : Please add

Studies in laboratoy animals (minipigs, rodents and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence od myocardial necrosis) when agonists and methylxanthanes are administered concurrently. The clinical significance of these findings is unknown.

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 and above dietary doses of 2 mg/kg (less than the maximum recommended daily oral dose for adults and children on a mg/m^2 basis). In another study this effect was blocked by the coadministration of propranolol, 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 65 times the maximum recommended daily oral dose for adults on a mg/m^2 basis and approximately 50 times the maximum recommended daily oral dose for children 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 8 times the maximum recommended daily oral dose for adults and children on a mg/m^2 basis).

Albuterol sulfate was not mutagenic in the Ames test with and without metabolic activation using tester strains S. Typhimurium TA 1537,TA 1538 or TA 98 or E coli WP_2, WP_2uvra and WP 67. No forward mutation was seen in yeast strain S. cerevisiae S_9 nor any mitotic gene conversion in yeast strain S. cerevisiae JD_1 with and without metabolic activation. Fluctuation assays in S. typhimurium TA 98 and E Coli WP_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.

Teratogenic Effects--Pregnancy Category C:.

In a study in CD-1 mice,

above 0.25 mg/kg (less than the maximum recommended daily oral dose for adults on a mg/m^2 basis) induced cleft palate formation in 5 of 111 (4.5%) fetuses. At a sc dose of 2.5 mg/kg (less than the maximum recommended daily oral dose for adults on a mg/m^2 basis), albuterol sulfate induced cleft formation in 10 of 108 (9.3%) fetuses. The drug did not induce cleft palate formation when administered at a sc dose of 0.025 mg/kg (significantly less than the maximum recommended daily oral 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. A reproduction study in Stride Dutch rabbits revealed cranioschesis in 7 of 19 (37%) fetuses when albuterol sulfate was administered orally at 50 mg/kg (approximately 25 times the maximum recommended daily oral dose for adults on a mg/m^2 basis).

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

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, albuterol 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 has not been established.

Overdosage :

The oral median lethal dose of albuterol sulfate in mice is greater than 2000 mg/kg (approximately 250 times the maximum recommended daily oral dose for adults on a mg/m^2 basis and approximately 200 times the maximun recommended daily oral dose for children on a mg/m^2 basis). In mature rats, the subcutaneous (sc) median lethal dose of albuterol sulfate is approximately 450 mg/kg (approximately 110 times the maximun recommended daily oral dose for adults on a mg/m^2 basis and approximately 90 times the maximun recommended daily oral dose for children on a mg/m^2 basis). In small young rats, the sc median lethal dose is

approximately 2000 mg/kg (approximately 510 times the maximum recommended daily oral dose for adults on a mg/m^2 basis and approximately 400 times the maximun recommended daily oral dose for children on a mg/m^2 basis).

The calculations for the labeling for Proventil Repetabs Tablets and Proventil tablets are listed below:

Drug:	**Proventil Repetabs and Tablets**						
	Age	mg/dose	# daily Doses	mg/day	kg	Mg/kg	factor	mg/m²
Pediatric	[redacted]			24	20	1.20	25	30.00
Adult	>12	[redacted]		32	50	0.64	37	23.68

	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	63.3446	50	65	50
Mouse			3	0	---	---	---	---
Mouse			3	0	---	---	---	---
Rat			6	12	0.50676	0.4	1/2	1/3
Hamster			4	200	8.44595	6.666667	8	7
Reproduction and Fertility:								
Rat	[redacted]		6	300	12.6689	N/A	15	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	0.00317	N/A	1/316	N/A
Mouse			3	0.75	0.03167	N/A	1/32	N/A
Mouse			3	7.5	0.31672	N/A	1/3	N/A
Rabbit			12	600	25.3378	N/A	25	N/A
Extra			---	---	---	N/A	---	N/A
Overdosage:								
Mouse	[redacted]		3	6000	253.378	200	250	200
Mouse			3	0	---	---	---	---
Rat			6	2700	114.02	90	110	90
Rat			6	12000	506.757	400	510	400
Other: (Describe studies here)								
Rat	[redacted]		6	0	---	---	---	---
Rat			6	0	---	---	---	---
Mouse			3	0	---	---	---	---
Mouse			3	0	---	---	---	---

Extra [redacted]	---	---	---	---	---	---

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		

Conclusion: Labeling revisions should be forwarded to the sponsor.

/S/

Virgil Whitehurst
Pharmacologist

10-19-98

/S/

Oct 19, 1998

CC:
Division File
HFD-570/JSun
HFD-570/VWhitehurst
HFD-570/BChowdhury
HFD-570/JParinda

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 17-559/S023
19-383/S010
17-853/S016

CORRESPONDENCE

JUN 24 1997

NDA 17-559/S-017, S-019, S-020, S-023

Schering Corporation
2000 Galloping Hill Road
Kenilworth, New Jersey 07033-0530

Attention: Joseph F. Lamendola, Ph.D.
Vice President
U.S. Regulatory Affairs

Dear Dr. Lamendola:

Please refer to your supplemental new drug applications dated January 3, 1989 (S-017), November 9, 1993 (S-019), April 14, 1995 (S-020) and December 23, 1996 (S-023), received January 10, 1989 (S-017), November 12, 1993 (S-019), April 18, 1995 (S-020), and December 24, 1996 (S-023), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Proventil (albuterol) Inhalation Aerosol.

We acknowledge receipt of your submissions dated June 1, 1989 (S-017), November 9, and 19, 1993, February 25, 1994 (S-019), and January 3, 1997 (S-023).

Supplement S-017 provides for revised Patient's Package Insert and HOW SUPPLIED section. This supplement has been superseded by Supplement S-023; therefore, it is being retained in our file.

Supplement S-019 provides for revised Pregnancy: Teratogenic Effects: Pregnancy Category C subsection of the PRECAUTIONS section. This supplement has been superseded by Supplement S-023; therefore, it is being retained in our file.

Supplement S-020 provides for revised Drug Interactions subsection of the PRECAUTIONS section. This supplement has been superseded by Supplement S-023; therefore, it is being retained in our file.

Supplement S-023 provides for revised labeling as requested by the Agency for all beta-agonists.

We have completed the review of supplement S-023 as submitted with draft labeling, and it is approvable. Before this supplement may be approved, however, it will be necessary for you to submit revised draft labeling. The labeling should include the changes in the enclosed marked-up draft labeling. In addition, the following information should be included:

1. The number of actuations delivered from the [redacted] g canister should be listed in the DESCRIPTION and HOW SUPPLIED sections.

2. The names of the mutagenic cell types used for the mutagenicity assays for albuterol sulfate should be included in the labeling.

3. The doses, duration of study, species name, and the route of administration for the carcinogenicity study in hamsters should be included in the labeling.

4. If available, all doses used in carcinogenicity and reproduction studies should be included in the labeling.

5. Please submit the reports of the mutagenicity assays for albuterol sulfate to your NDA.

6. The color of the mouthpiece and the cap should be specified in HOW SUPPLIED section.

7. The term "test spray" in the DOSAGE AND ADMINISTRATION SECTION, and in item 2 of the Patient's Package Insert should be more clearly defined based on the data. This should include the number of sprays needed for priming, and how long an interval may pass before repriming.

To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

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

Sincerely yours,

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

Enclosure: Marked-up draft labeling

13 **Page(s) Redacted**

Draft

Labeling