CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 76-130

***Name*:** Albuterol Extended-release Tablets, 4 mg and 8 mg

***Sponsor*:** Sidmak Laboratories, Inc.

***Approval Date*:** September 26, 2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-130

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-130

APPROVAL LETTER

ANDA 76-130

SEP 26 2002

Sidmak Laboratories, Inc.
Attention: Deborah L. Pakay
17 West Street
P.O. Box 371
East Hanover, NJ 07936

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated March 2, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Albuterol Extended-release Tablets, 4 mg and 8 mg.

Reference is also made to your amendments dated July 19, and August 3, 2001; and May 21, May 31, June 21, and September 23, 2002. We also refer to your communications dated May 15 and June 22, 2001, pertaining to patent issues related to the approval of the drug product.

The listed drug product (RLD) referenced in your application, Volmax Extended-release Tablets of Muro Pharmaceutical, Inc., is subject to periods of patent protection. As noted in the agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations, the "Orange Book", these patents are scheduled to expire on June 14, 2005 (U.S. Patent Nos. 4,751,071 (the '071 patent) and 4,851,229 (the '229 patent) and October 11, 2005 (U.S. Patent No. 4,777,049 (the '049 patent). Your application contains patent certifications to each of these patents under Section 505(j)(2)(A)(vii)(IV) of the Act stating that the patents are invalid and/or will not be infringed by the manufacture, use, or sale of your drug product. Section 505(j)(5)(B)(iii) of the Act provides that approval of an ANDA shall be made effective immediately, unless an action is brought against Sidmak Laboratories Inc. (Sidmak) for infringement of one or more of the listed patents that are the subject of the "paragraph IV certifications". Such action must be brought against Sidmak before the expiration of forty-five (45) days from the date the notice you provided to the NDA/patent holder(s) under paragraph (2)(B)(i) was received.

You have notified FDA that Sidmak complied with the requirements of Section 505(j)(2)(B) of the Act, and that no action for patent infringement was brought against Sidmak within the statutory forty-five day period.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Albuterol Extended-release Tablets, 4 mg and 8 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug, Volmax® Extended-release Tablets, 4 mg and 8 mg, of Muro Pharmaceutical Inc. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application. The "interim" dissolution specifications for both strengths of the drug are as follows:

Time (Hr)	% Dissolution
2	[redacted]
4	[redacted]
6	[redacted]
8	NLT [redacted]

The in vitro dissolution testing should be conducted in 900 mL of de-ionized water using USP apparatus 2 (paddle) at 50 rpm.

The "interim" dissolution test(s) and tolerances should be finalized by submitting dissolution data for the first three production size batches. Data should be submitted as a Special Supplement - Changes Being Effected when there are no revisions to the "interim" specifications or when the final specifications are tighter than the "interim" specifications. In all other instances, the information should be submitted in the form of a Prior Approval Supplement.

Furthermore, we note that Sidmak was the first applicant to submit a substantially complete ANDA containing "paragraph IV certifications" to the listed patents for this drug product.

Therefore, with this approval, Sidmak is eligible for 180-days of market exclusivity for each strength as provided for under the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments) in Section 505(j)(5)(B)(iv) of the Act. Such exclusivity will begin to run on the date Sidmak begins commercial marketing.

With respect to the "first commercial marketing" trigger for the commencement of exclusivity, please refer to 21 CFR 314.107 (c)(4). The agency expects that you will begin commercial marketing of this drug product in a prompt manner. Please submit correspondence to your application stating the date you commenced commercial marketing of the product.

If you have any questions concerning the effective date of approval of an ANDA and the agency's elimination of the requirement that an ANDA applicant successfully defend a patent infringement suit to be eligible for 180-days of marketing exclusivity, please refer to the interim rule published in the November 5, 1998 Federal Register (Volume 63, No. 214, 59710).

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy that you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Gary Buehler 9/26/02
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-130
Division File
Field Copy
HFD-610/R. West
HFD-210/B. Poole
HFD-330
HFD-205
HFD-92

Endorsements:
HFD-645/D.Maldonado/ DMR 8/16/02.
HFD-645/B.Arnwine/8/15/02 (31 comments) 8/19/02
HFD-617/N.Park/ NPark 8/19/02
HFD-613/A.Payne/ APayne 8/18/02 no changes in labeling
HFD-613/J.Grace/ Grace for J. Grace 8/19/02

Robert Lupfest
9/26/2002

v:/firmsnz/sidmak/ltrs&rev/76130d.ap
F/T by rad8/16/02

APPROVAL
PACT

cmc satisfactory.
Lloyd Y. Tsuyuki
8/21/02.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-130

LABELING

SEP 30 2002

APPROVED

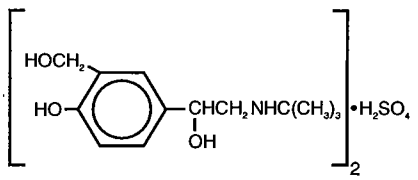
080645

P08-0645

ALBUTEROL EXTENDED-RELEASE TABLETS

Rx only Rev. 1/02

DESCRIPTION: Albuterol extended-release tablets contain albuterol sulfate, the racemic form of albuterol and a relatively selective beta$_2$-adrenergic bronchodilator, in an extended-release formulation. 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 structural formula:



Albuterol sulfate has a molecular weight of 576.7, and the molecular formula is $(C_{13}H_{21}NO_3)_2 \bullet H_2SO_4$. 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 tablet for oral administration contains 4 mg or 8 mg of albuterol as 4.8 mg or 9.6 mg, respectively, of albuterol sulfate in a cellulosic material that serves as a diffusion-release membrane. In addition each tablet contains the following inactive ingredients: Calcium sulfate, carnauba wax, ethylcellulose, ferric oxide black, hydroxypropyl methylcellulose, ink-thinner XI, lactose monohydrate, magnesium stearate, polyethylene glycol, propylene glycol, shellac, stearic acid, titanium dioxide, triacetin, D&C Yellow #10, and FD&C Blue #1.

CLINICAL PHARMACOLOGY: *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 indicates 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. (See Warnings).

The pharmacologic effects of beta-adrenergic agonist drugs, including albuterol, are at least in part attributable to stimulation through beta-adrenergic receptors on intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3′, 5′-adenosine monophosphate (cyclic AMP). 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.

Albuterol has been shown in most controlled clinical trials to have more effect on the respiratory tract, in the form of bronchial smooth muscle relaxation, than isoproterenol at comparable doses while producing fewer cardiovascular effects.

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 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 were administered concurrently. The clinical significance of these findings is unknown.

Pharmacokinetics and Disposition: In a single-dose study comparing one 8 mg albuterol extended-release tablet with two 4 mg immediate-release albuterol tablets, USP in 17 normal adult volunteers, the extent of availability of albuterol extended-release tablets was shown to be about 80% of albuterol tablets, USP with or without food. In addition, lower mean peak plasma concentration and longer time to reach the peak level were observed with albuterol extended-release tablets as compared with albuterol tablets, USP. The single-dose study results also showed that food decreases the rate of absorption of albuterol from albuterol extended-release tablets without altering the extent of bioavailability. In addition, the study indicated that food causes a more gradual increase in the fraction of the available dose absorbed from the extended-release formulation as compared with the fasting condition.

In another single-dose study in adults, 8 mg and 4 mg albuterol extended-release tablets were shown to deliver dose-proportional plasma concentrations in the fasting state. Definitive studies for the effect of food on 4 mg albuterol extended-release tablets have not been conducted. However, since food lowers the rate of absorption of 8 mg albuterol extended-release tablets, it is expected that food reduces the rate of absorption of 4 mg albuterol extended-release tablets also.

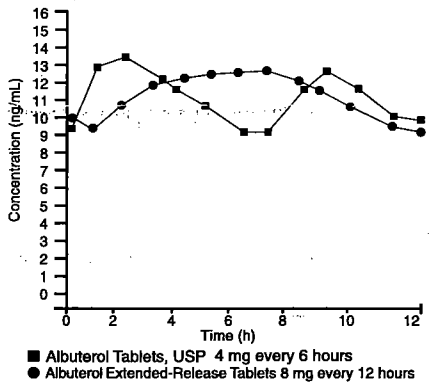
Albuterol extended-release tablets have been formulated to provide duration of action of up to 12 hours. In an 8-day, multiple-dose, crossover study, 15 normal adult male volunteers were given 8 mg albuterol extended-release tablets every 12 hours or 4 mg albuterol tablets, USP every 6 hours. Each dose of albuterol extended-release tablets and the corresponding doses of albuterol tablets, USP were administered in the postprandial state. Steady-state plasma concentrations were reached within 2 days for both formulations. Fluctuations (C_{max}-C_{min}/$C_{average}$) in plasma concentrations were similar for albuterol extended-release tablets administered at 12-hour intervals and albuterol tablets, USP administered every 6 hours. In addition, the relative bioavailability of albuterol extended-release tablets was approximately 100% of the immediate-release tablet at steady state. A summary of these results is shown in the following table:

Mean Values at Steady State

	C_{max} (ng/mL)	C_{min} (ng/mL)	T_{max} (h)	$T_{1/2}$ (h)	AUC (ng-h/mL)
Albuterol Extended-Release Tablets	13.7	8.1	6.0	9.3	134
Albuterol Tablets, USP	13.9	8.1	2.6	7.2	132

The mean plasma albuterol concentration versus time data at steady state after the administration of albuterol extended-release tablets 8 mg every 12 hours are displayed in the following graph:

Mean Plasma Albuterol Concentration at Day 8



Pharmacokinetic studies of 4- and 8-mg albuterol extended-release tablets have not been conducted in pediatric patients. Bioavailability of 4- and 8-mg albuterol extended-release tablets in pediatric patients relative to 2- and 4-mg immediate release albuterol has been extrapolated from adult studies showing comparability at steady-state dosing and reduced bioavailability after single dose administration.

INDICATIONS AND USAGE: Albuterol extended-release tablets are indicated for the relief of bronchospasm in adults and children 6 years of age and older with reversible obstructive airway disease.

CONTRAINDICATIONS: Albuterol extended-release tablets are contraindicated in patients with a history of hypersensitivity to albuterol or any of its components.

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

Cardiovascular Effects: Albuterol extended-release 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 albuterol extended-release 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 QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Therefore, albuterol extended-release tablets, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

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 albuterol extended-release tablets than usual, this may be a marker of destabilization of asthma and requires reevaluation of the patient and the treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment; e.g., corticosteroids.

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; e.g., corticosteroids.

Paradoxical Bronchospasm: Albuterol extended-release tablets can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs, albuterol extended-release tablets should be discontinued immediately and alternative therapy instituted.

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

In controlled clinical trials in adults, patients treated with albuterol extended-release tablets had increases in selected serum chemistry values and decreases in selected hematologic values. Increases in SGPT were more frequent among patients treated with albuterol extended-release tablets (12 of 247 patients, 4.9%) than among the theophylline (6 of 188 patients, 3.2%) and placebo (1 of 138 patients, 0.7%) groups. Increases in serum glucose concentration were also more frequent among patients treated with albuterol extended-release tablets (23 of 234 patients, 9.8%) than among theophylline (11 of 173 patients, 6.45%) and placebo (3 of 129 patients, 2.3%) groups. Increases in SGOT were also more frequent among patients treated with albuterol extended-release tablets (10 of 248 patients, 4%) and theophylline (5 of 193, 2.6%) than among patients treated with placebo. Decreases in white blood cell counts were more frequent in patients treated with albuterol extended-release tablets (10 of 247 patients, 4%) compared with patients receiving theophylline (2 of 185 patients, 1.1%) and patients receiving placebo (1 of 141 patients, 0.7%). Decreases in hemoglobin and hematocrit were more frequent in patients receiving albuterol extended-release tablets (16 of 228 patients, 7.0%, and 17 of 230 patients, 7.4%, respectively) than in patients receiving theophylline (5 of 171 patients, 2.9%, and 9 of 173 patients, 5.2%, respectively) and patients receiving placebo (5 of 129 patients, 3.9%, and 3 of 132 patients, 2.3%, respectively). The clinical significance of these results is unknown.

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:

Albuterol extended-release tablets must be swallowed whole with the aid of liquids. DO NOT CHEW OR CRUSH THESE TABLETS.

The action of albuterol extended-release tablets should last up to 12 hours or longer. Albuterol extended-release tablets should not be used more frequently than recommended. Do not increase the dose or frequency of albuterol extended-release tablets without consulting your physician. If you find that treatment with albuterol extended-release tablets 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 albuterol extended-release 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 use of albuterol extended-release tablets. Effective and safe use of albuterol extended-release tablets includes an understanding of the way that it should be administered.

Drug Interactions: The concomitant use of albuterol extended-release 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 albuterol extended-release 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.

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.

Beta Blockers: Beta-adrenergic receptor blocking agents not

only block the pulmonary effect of beta-agonists, such as albuterol extended-release 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, e.g., 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 non potassium-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 non potassium-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 these findings for patients with obstructive airway disease who are receiving albuterol and digoxin on a chronic basis is unclear. Nevertheless, it would be prudent to carefully evaluate the serum digoxin levels in patients who are currently receiving digoxin and albuterol.

CARCINOGENESIS, MUTAGENESIS, 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 dietary doses of 2.0, 10, and 50 mg/kg, (approximately 1/2, 3, and 15 times, respectively, the maximum recommended daily oral dose for adults on a mg/m² basis, or, approximately 2/5, 2, and 10 times, respectively, the maximum recommended daily oral dose for children on a mg/m² 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 of up to 500 mg/kg (approximately 65 times the maximum recommended daily oral dose for adults on a mg/m² basis, or, approximately 50 times the maximum recommended daily oral dose for children on a mg/m² basis). In a 22 month study in the Golden hamster, albuterol sulfate showed no evidence of tumorigenicity at dietary doses of 50 mg/kg, (approximately 7 times the maximum recommended daily oral dose for adults and children on a mg/m² basis).

Albuterol sulfate was not mutagenic in the Ames test with or without metabolic activation using tester strains *S. typhimurium* TA 1537, TA 1538, and TA98 or *E. coli* WP2, WP2uvrA, and WP67. No forward mutation was seen in yeast strain *S. cerevisiae* S9 nor any mitotic gene conversion in yeast strain *S. cerevisiae* JD1 with or without metabolic activation. Fluctuation assays in *S. typhimurium* TA98 and *E. coli* WP2, both with metabolic activation, were negative. Albuterol sulfate was not clastogenic in a human peripheral lymphocyte assay or in an AH1 strain mouse micronucleus assay at intraperitoneal doses of up to 200 mg/kg.

Reproduction studies in rats demonstrated no evidence of impaired fertility at oral doses up to 50 mg/kg, (approximately 15 times the maximum recommended daily oral dose for adults on a mg/m² basis).

Pregnancy: 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 of 0.025, 0.25, and 2.5 mg/kg, (approximately 3/1000, 3/100, and 3/10 times the maximum recommended daily oral dose for adults on a mg/m² basis), showed cleft palate formation in 5 of 111 (4.5%) fetuses at 0.25 mg/kg and in 10 of 108 (9.3%) fetuses at 2.5 mg/kg. The drug did not induce cleft palate formation at the lowest dose, 0.025 mg/kg. Cleft palate also occurred in 22 of 72 (30.5%) fetuses of females treated with 2.5 mg/kg, of isoproterenol (positive control) subcutaneously (approximately 3/10 times the maximum recommended daily oral dose for adults on a mg/m² basis). A reproduction study in Stride Dutch rabbits revealed cranioschisis in 7/19 fetuses (37%) when albuterol sulfate was administered orally at a 50 mg/kg dose, (approximately 25 times the maximum recommended daily oral dose for adults on a mg/m² basis).

There are no adequate and well-controlled studies in pregnant women. 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 rarely reported in the offspring of patients being treated with albuterol. Some of the mothers were taking multiple medications during their pregnancies. No consistent pattern of defects can be discerned, and a relationship between albuterol use and congenital anomalies has not been established.

Labor and Delivery: Because of the potential for beta-agonist interference with uterine contractility, use of albuterol extended-release tablets for relief of bronchospasm during labor should be restricted to those patients in whom the benefits clearly outweigh the risks.

Tocolysis: Albuterol has not been approved for the management of pre-term labor. The benefit:risk ratio when albuterol is administered for tocolysis has not been established. Serious adverse reactions, including pulmonary edema, have been reported during or following treatment of premature labor with $beta_2$-agonists, including albuterol.

Nursing Mothers: It is not known whether albuterol is excreted in human milk. Because of the potential for tumorigenicity shown for albuterol in 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 albuterol extended-release tablets have been established in pediatric patients 6 years of age or older. Use of albuterol extended-release tablets in these age groups is supported by evidence from adequate and well-controlled studies of albuterol extended-release 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 immediate release albuterol tablets in pediatric patients 6 years of age and older; and clinical trials that support the safety of albuterol extended-release tablets in pediatric patients over 6 years of age. The recommended dose of albuterol extended-release tablets for the pediatric population is based upon the recommended pediatric dosing of immediate-release albuterol tablets and pharmacokinetic studies in adults showing comparable bioavailability at steadystate dosing and reduced bioavailability after single dose administration. Safety and effectiveness in pediatric patients below 6 years of age have not been established.

ADVERSE REACTIONS: The adverse reactions to albuterol are similar in nature to reactions to other sympathomimetic agents. The most frequent adverse reactions to albuterol are nervousness, tremor, headache, tachycardia, and palpitations. Less frequent adverse reactions are muscle cramps, insomnia, nausea, weakness, dizziness, drowsiness, flushing, restlessness, irritability, chest discomfort, and difficulty in micturition.

Rare cases of urticaria, angioedema, rash, bronchospasm, and oropharyngeal edema have been reported after the use of albuterol.

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

In controlled clinical trials of adult patients conducted in the United States, the following incidence of adverse events was reported:

	Albuterol Extended-Release Tablets	Theophylline	Other Beta-agonists	Placebo
Event (*n*=330)	(*n*=197)	(*n*=20)	(*n*=178)	
Tremor	24.2%	6.1%	35.0%	1.1%
Headache	18.8%	26.9%	35.0%	20.8%
Nervousness	8.5%	5.1%	10.0%	2.8%
Nausea/Vomiting	4.2%	19.8%	5.0%	3.9%
Tachycardia	2.7%	0.5%	5.0%	0%
Muscle Cramps	2.7%	0.5%	5.0%	0.6%
Palpitations	2.4%	0.5%	0%	1.1%
Insomnia	2.4%	6.1%	0%	1.7%
Dizziness	1.5%	2.0%	0%	5.1%
Somnolence	0.3%	1.0%	0%	0.6%

A trend was observed among patients treated with albuterol extended-release tablets toward increasing frequency of muscle cramps with increasing patient age (12-20 years, 1.2%; 21-30 years, 2.6%; 31-40 years, 6.9%; 41-50 years, 6.9%), compared with no such events in the placebo group. Also observed was an increasing frequency of tremor with increasing patient age (12-20 years, 29.4%; 21-30 years, 29.9%; 31-40 years, 27.6%; 41-50 years, 37.9%), compared to 2.9% or less in the placebo group.

The reactions are generally transient in nature, and it is usually not necessary to discontinue treatment with albuterol extended-release tablets.

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; e.g., seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats per minute, arrhythmias, nervousness, headache, tremor, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and insomnia. Hypokalemia may also occur. As with all sympathomimetic aerosol medications, cardiac arrest and even death may be associated with abuse of albuterol extended-release tablets.

Treatment consists of discontinuation of albuterol extended-release 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 albuterol extended-release 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 a mg/m² basis, or, approximately 200 times the maximum recommended daily oral dose for children on a mg/m² basis). In mature rats, the subcutaneous median lethal dose of albuterol sulfate is approximately 450 mg/kg (approximately 110 times the maximum recommended daily oral dose for adults on a mg/m² basis, or, approximately 90 times the maximum recommended daily oral dose for children on a mg/m² basis). In small young rats, the subcutaneous median lethal dose is approximately 2000 mg/kg, (approximately 500 times the maximum recommended daily oral dose for adults on a mg/m² basis, or, approximately 400 times the maximum recommended daily oral dose for children on a mg/m² basis).

DOSAGE AND ADMINISTRATION: The following dosages of albuterol extended-release tablets are expressed in terms of albuterol base:

Usual Dosage:

Adults and Children over 12 years of age: The usual recommended dosage for adults and pediatric patients over 12 years of age is 8 mg every 12 hours. In some patients, 4 mg every 12 hours may be sufficient.

Children 6 to 12 years of age: The usual recommended dosage for children 6 through 12 years of age is 4 mg every 12 hours.

Dosage adjustment in Adults and Children over 12 years of age: In unusual circumstances, such as adults of low body weight, it may be desirable to use a starting dosage of 4 mg every 12 hours and progress to 8 mg every 12 hours according to response.

If control of reversible airway obstruction is not achieved with the recommended doses in patients on otherwise optimized asthma therapy, the doses may be cautiously increased stepwise under the control of the supervising physician to a maximum dose of 32 mg per day in divided doses (i.e., every 12 hours).

Dosage adjustment in Children 6 to 12 years of age: If control of reversible airway obstruction is not achieved with the recommended doses in patients on otherwise optimized asthma therapy, the doses may be cautiously increased stepwise under the control of the supervising physician to a maximum dose of 24 mg per day in divided doses (i.e., every 12 hours).

Switching from oral albuterol, USP products: Patients currently maintained on albuterol tablets, USP or albuterol sulfate syrup can be switched to albuterol extended-release tablets. For example, the administration of one 4 mg albuterol extended-release tablet every 12 hours is comparable to one 2 mg albuterol tablet, USP every 6 hours. Multiples of this regimen up to the maximum recommended daily dose also apply.

Albuterol extended-release tablets must be swallowed whole with the aid of liquids. **DO NOT CHEW OR CRUSH THESE TABLETS.**

HOW SUPPLIED: Albuterol Extended-Release Tablets, equivalent to 4 mg and 8 mg of Albuterol:

4 mg - Green, round, coated tablets in bottles of 100 and 500. Printed SL on one side and 45 on the other side in black ink.

8 mg - Green, round, coated tablets in bottles of 100 and 500. Printed SL on one side and 46 on the other side in black ink.

Dispense in a well-closed, light-resistant container as defined in the USP. Replace cap securely after each opening. Store at controlled room temperature 15°-30°C (59°-86°F).

Manufactured by:
SIDMAK LABORATORIES, INC.
East Hanover, NJ 07936

P08-0645 Rev. 1/02
c/n

NDC 50111-645-01

Albuterol Extended-Release Tablets

(oral) 4 mg*

Rx only

100 Tablets

Sidmak LABORATORIES, INC.

*Each extended-release tablet contains 4.8 mg of albuterol sulfate equivalent to 4 mg albuterol tablets.

Dispense in a well-closed, light-resistant container as defined in the USP. Replace cap securely after each opening.

Store at controlled room temperature 15°-30°C (59°-86°F).

USUAL DOSAGE: See package insert.

Tablets must be swallowed whole with the aid of liquids.

Do not chew or crush.

Control No.:

Exp. Date: SEP 30 2002

Rev. 1/02

APPROVED

SIDMAK LABORATORIES, INC.
East Hanover, NJ 07936

3 50111-645-01 1

NDC 50111-645-02

Albuterol Extended-Release Tablets

(oral) 4 mg*

Rx only

500 Tablets

Sidmak LABORATORIES, INC.

*Each extended-release tablet contains 4.8 mg of albuterol sulfate equivalent to 4 mg albuterol tablets.

Dispense in a well-closed, light-resistant container as defined in the USP. Replace cap securely after each opening.

Store at controlled room temperature 15°-30°C (59°-86°F).

USUAL DOSAGE: See package insert.

Tablets must be swallowed whole with the aid of liquids.

Do not chew or crush. SEP 30 2002

Control No.:

Exp. Date:

Rev. 1/02 APPROVED

SIDMAK LABORATORIES, INC.
East Hanover, NJ 07936

3 50111-645-02 8

NDC 50111-646-01

Albuterol Extended-Release Tablets

(oral) 8 mg*

Rx only

100 Tablets

Sidmak LABORATORIES, INC.

*Each extended-release tablet contains 9.6 mg of albuterol sulfate equivalent to 8 mg albuterol tablets.
Dispense in a well-closed, light-resistant container as defined in the USP. Replace cap securely after each opening.
Store at controlled room temperature 15°-30°C (59°-86°F).
USUAL DOSAGE: See package insert.
Tablets must be swallowed whole with the aid of liquids.
Do not chew or crush.

SEP 30 2002

Control No.:
Exp. Date:
Rev. 1/02

APPROVED

SIDMAK LABORATORIES, INC.
East Hanover, NJ 07936

N 3 50111-646-01 8

NDC 50111-646-02

Albuterol Extended-Release Tablets

(oral) 8 mg*

Rx only

500 Tablets

Sidmak LABORATORIES, INC.

*Each extended-release tablet contains 9.6 mg of albuterol sulfate equivalent to 8 mg albuterol tablets.
Dispense in a well-closed, light-resistant container as defined in the USP. Replace cap securely after each opening.
Store at controlled room temperature 15°-30°C (59°-86°F).
USUAL DOSAGE: See package insert.
Tablets must be swallowed whole with the aid of liquids.
Do not chew or crush.

SEP 30 2002

Control No.:
Exp. Date:
Rev. 1/02

APPROVED

SIDMAK LABORATORIES, INC.
East Hanover, NJ 07936

N 3 50111-646-02 5

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-130

LABELING REVIEWS

REVIEW OF PROFESSIONAL LABELING #1 (first generic)
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **76-130** Date of Submission: March 2, 2001
Applicant's Name: Sidmak Laboratories, Inc.
Established Name: **Albuterol Extended-release Tablets, 4 mg and 8 mg**

Labeling Deficiencies:

1. GENERAL COMMENT: Please revise all labels and labeling to read "Albuterol Extended-release Tablets " rather than Albuterol Sulfate Extended-release Tablets.
2. CONTAINER (4 mg and 8 mg) 100s and 500s
   a. Please increase the prominence of " do not chew or crush".
   b. Revise each strength and the each tablet contain statement as follows:
      "(oral) 4 mg*.
      *Each extended-release tablet contains 4.8 mg of albuterol sulfate equivalent to 4 mg albuterol tablets.
3. [redacted] See comments under GENERAL COMMENTS and CONTAINER.
4. INSERT
   a. GENERAL COMMENT – Revise "[redacted] tablets" to read " Albuterol tablets, USP" throughout the insert.
   b. DESCRIPTION – revise "[redacted] ' to read "structural formula".
   c. HOW SUPPLIED - You may delete reference to the Ventolin trademark information.

Please revise your labels and labeling, as instructed above, and submit 12 copies of final printed labels and labeling.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes - http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Wm. Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):Do you have 12 Final Printed Labels and Labeling? Yes No If no, list why:
Container Labels:
Carton Labeling:
Professional Package Insert Labeling:
Patient Package Insert Labeling:
Revisions needed post-approval:
BASIS OF APPROVAL:

Patent Data For NDA 19-604

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4851229	June 14, 2005		Composition comprising a therapeutic agent and a modulating agent	P-IV	
4751071	June 14, 2005		Composition comprising salbutamol	P-IV	
4777049	Oct 11, 2005		Constant release system with pulsed release	P-IV	

Exclusivity Data For NDA: There are no unexpired protections

Code/sup	Expiration	Use Code	Description		Labeling Impact
					SAME AS

Was this approval based upon a petition? No
What is the RLD on the 356(h) form: VOLMAX
NDA Number: 19-604
NDA Drug Name: Albuterol sulfate extended release tablets
NDA Firm: Muro
Date of Approval of NDA Insert and supplement #: s-007 approved April 6, 99
Has this been verified by the MIS system for the NDA? No
Was this approval based upon an OGD labeling guidance? No
If yes, give date of labeling guidance:
Basis of Approval for the Container Labels: container in application

Other Comments: We believe the name should be consistent with the USP Monograph for Albuterol Tablets.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N/A
Different name than on acceptance to file letter?	X		
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	X tabs	X ER	
Is this name different than that used in the Orange Book?	X	X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?		X	
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X

Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N/A
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?	X		
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.	X		
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

1. Review based on the labeling of NDA 19604 Volmax (S/007, revised 4-99; approved 4/6/99). Under the PRECAUTION section (4th paragraph under the General subsection and the 1st and 2nd paragraphs under Information for Patients were deleted. Because applicant delivery system is different . The applicant product is extended release but does not leave behind an outer shall in the stool (nondeformable material). CLINCIAL PHARMACOLOGY section. Since this is a product whose bio avialablity is difficult to match I suggest that we use the phrase ———————— .

3. Storage Conditions:
   NDA - store between 2 to 30C
   ANDA –CRT 15-30 C
   USP -
4. Dispensing Recommendations:
   NDA -
   ANDA- Dispense in a well-closed, light-resistant container. Replace the cap securely after each opening.
   USP - Well-closed light-resistant container
5. Scoring:
   NDA – not scored
   ANDA – not scored
   USP -
6. Product Line:
   The innovator markets their product in HDPE bottles with CRC 100s, and 500s.
   The applicant proposes to market their product in 100s and 500s
7. The tablet/capsule imprint(ings)/embossing(s)/ debossing(s) has/have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). Yes page 1366 red volume 1.3
8. Inactive Ingredients:
   The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 264(Volume 1.1 red) .
9. Bio pending.
10. Manufactured by sidmake lab
11. The naming of this product should be consistent with the USP monograph for the tablets. The name should be changed from Albuterol Sulfate ER tablets to Albuterol ER tablets, 4 mg or 8 mg *. (* equivalent to 4.8 mg of albuterol sulfate.)

Date of Review: May 21, 01 **Date of Submission: March 2, 2001**

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cc: ANDA: 76-130
DUP/DIVISION FILE
HFD-613/apayne/ gracej (no cc)
V:firmsnz/sidmak/lets&revs/76130na1.L
Review

1/02/01
1/2/2002

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number	76-130
Date of Submission	Jan. 22, 2002
Applicant	Sidmak labs.
Drug Name	Albuterol Extended-release Tablets
Strength(s)	4 mg, 8 mg

FPL Approval Summary		
Container Labels		
4 mg	100s, 500s	submitted January 22, 2002 vol. 2.1 blue
8 mg	100s, 500s	Submitted January 22, 2002 vol. 2.1 blue
Package Insert Labeling	P080645 Rev. Date Jan. 2002	Submitted January 22, 2002 vol. 2.1 blue

BASIS OF APPROVAL:

Patent Data For NDA 19-604

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4851229	June 14, 2005	------	Composition comprising a therapeutic agent and a modulating agent	P-IV	No impact
4751071	June 14, 2005	-----	Composition compring salbutamol	PIV	No impact
4777049	Oct 11, 2005	-----	Constant release system with pulsed release	P-IV	No impact

Exclusivity Data For NDA 19-604			
Code/sup	**Expiration**	**Description**	**Labeling impact**
		None	

Reference Listed Drug

RLD on the 356(h) form	Volmax® Tablets
NDA Number	19-604
RLD established name	Albuterol sulfate extended-release tablets
Firm	Muro
Currently apprvoved PI	S-007
AP Date	Nov. 20, 1997

Note: FPL approved April 6, 1999

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N/A
Different name than on acceptance to file letter?	X		
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	X tabs	X ER	
Is this name different than that used in the Orange Book?	X	X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?		X	
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N/A
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?	X		
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	

Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.	X		
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	X		

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

1. Review based on the labeling of NDA 19604 Volmax (S/007, revised 4-99; approved 4/6/99). Under the PRECAUTION section (4th paragraph under the General subsection and the 1st and 2nd paragraphs under Information for Patients were deleted. Because applicant delivery system is different . The applicant product is extended release but does not leave behind an outer shall in the stool (nondeformable material). CLINCIAL PHARMACOLOGY section.
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   NDA -
   ANDA- Dispense in a well-closed, light-resistant container. Replace the cap securely after each opening.
   USP - Well-closed light-resistant container
5. Scoring:
   NDA – not scored
   ANDA – not scored
   USP -
6. Product Line:
   The innovator markets their product in HDPE bottles with CRC 100s, and 500s.
   The applicant proposes to market their product in 100s and 500s
7. The tablet/capsule imprint(ings)/embossing(s)/ debossing(s) has/have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). Yes page 1366 red volume 1.3
8. Inactive Ingredients:
   The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 264(Volume 1.1 red) .
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10. Manufactured by sidmake lab
11. The naming of this product should be consistent with the USP monograph for the tablets. The name should be changed from Albuterol Sulfate ER tablets to Albuterol ER tablets, 4 mg or 8 mg *. (* equivalent to 4.8 mg of albuterol sulfate.)

Date of Review: **February 06, 2002**

Date of Submission: **January 22, 2002**

cc: ANDA: 76-130
DUP/DIVISION FILE
HFD-613/apayne/ gracej (no cc)
V:firmsnz/sidmak/lets&revs/76130.apL
Review

2/06/02

3/6/2002