

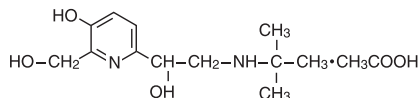
# MAXAIR® AUTOHALER®

(pirbuterol acetate inhalation aerosol)

## For Oral Inhalation Only

### DESCRIPTION

The active component of MAXAIR AUTOHALER (pirbuterol acetate) is (R,S) $\alpha^6$ -[(1,1-dimethylethyl)amino]methyl]-3-hydroxy-2,6-pyridinedimethanol monoacetate salt, a beta-2 adrenergic bronchodilator, having the following chemical structure:



Pirbuterol acetate is a white, crystalline racemic mixture of two optically active isomers. It is a powder, freely soluble in water, with a molecular weight of 300.3 and empirical formula of  $C_{12}H_{20}N_2O_3 \cdot C_2H_4O_2$ .

MAXAIR AUTOHALER is a pressurized metered-dose aerosol unit for oral inhalation. It provides a fine-particle suspension of pirbuterol acetate in the propellant mixture of trichloromonofluoromethane and dichlorodifluoromethane, with sorbitan trioleate. Each actuation delivers 253 mcg of pirbuterol (as pirbuterol acetate) from the valve and 200 mcg of pirbuterol (as pirbuterol acetate) from the mouthpiece. The unit is breath-actuated such that the medication is delivered automatically during inspiration without the need for the patient to coordinate actuation with inspiration. Each 14.0 g canister provides 400 inhalations and each 2.8 g canister provides 80 inhalations.

As with all aerosol medications, it is recommended to prime (test) MAXAIR AUTOHALER before using for the first time. MAXAIR AUTOHALER should also be primed if it has not been used in 48 hours. As described in the priming procedure, use the test fire slide to release two priming sprays into the air away from yourself and other people. (See "Patient's Instructions For Use" portion of this package insert.)

### CLINICAL PHARMACOLOGY

*In vitro* studies and *in vivo* pharmacologic studies have demonstrated that pirbuterol 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 10-50%. The precise function of these receptors has not been established (see WARNINGS section).

The pharmacologic effects of beta adrenergic agonist drugs, including pirbuterol, are at least in part attributable to stimulation through beta adrenergic receptors of intracellular adenylyl cyclase, the enzyme which catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (c-AMP). Increased c-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.

Bronchodilator activity of pirbuterol was manifested clinically by an improvement in various pulmonary function parameters ( $FEV_1$ , MMF, PEFR, airway resistance [RAW] and conductance [ $GA/V_{50}$ ]).

**Clinical Trials:** In controlled double-blind single-dose clinical trials, the onset of improvement in pulmonary function occurred within 5 minutes in most patients as determined by forced expiratory volume in one second ( $FEV_1$ ).  $FEV_1$  and MMF measurements also showed that maximum improvement in pulmonary function generally occurred 30-60 minutes following one (1) or two (2) inhalations of pirbuterol (200-400 mcg). The duration of action of pirbuterol is maintained for 5 hours (the time at which the last observations were made) in a substantial number of patients, based on a 15% or greater increase in  $FEV_1$ . In controlled repetitive-dose studies of 12 weeks' duration, 74% of 156 patients on pirbuterol and 62% of 141 patients on metaproterenol showed a clinically significant improvement based on a 15% or greater increase in  $FEV_1$  on at least half of the days. Onset and duration were equivalent to that seen in single-dose studies. Continued effectiveness was demonstrated over the 12-week period in the majority (94%) of responding patients; however, chronic dosing was associated with the development of tachyphylaxis (tolerance) to the bronchodilator effect in some patients in both treatment groups.

A placebo-controlled, double-blind, single-dose study (24 patients per treatment group), utilizing continuous Holter monitoring for 5 hours after drug administration, showed no significant difference in ectopic activity between the placebo control group and pirbuterol at the recommended dose (200-400 mcg), and twice the recommended dose (800 mcg). As with other inhaled beta adrenergic agonists, supraventricular and ventricular ectopic beats have been seen with pirbuterol (see WARNINGS).

Two randomized, double-blind, cross-over studies in a total of 97 patients, have compared the clinical effects of either one inhalation or two inhalations of the pirbuterol formulations in the AUTOHALER actuator and the conventional inhaler and demonstrated no significant difference between the formulations for the means of peak changes in  $FEV_1$ , time to peak  $FEV_1$ , onset, duration, or area under the  $FEV_1$  curve.

**Preclinical:** 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 when applied to humans is unknown.

**Pharmacokinetics:** As expected by extrapolation from oral data, systemic blood levels of pirbuterol are below the limit of assay sensitivity (2-5 ng/ml) following inhalation of doses up to 800 mcg (twice the maximum recommended dose). A mean of 51% of the dose is recovered in urine as pirbuterol plus its sulfate conjugate following administration by aerosol. Pirbuterol is not metabolized by catechol-O-methyltransferase.

The percent of administered dose recovered as pirbuterol plus its sulfate conjugate does not change significantly over the dose range of 400 mcg to 800 mcg and is not significantly different from that after oral administration of pirbuterol. The plasma half-life measured after oral administration is about two hours.

### INDICATIONS AND USAGE

MAXAIR AUTOHALER is indicated for the prevention and reversal of bronchospasm in patients 12 years of age and older with reversible bronchospasm including asthma. It may be used with or without concurrent theophylline and/or corticosteroid therapy.

### CONTRAINDICATIONS

MAXAIR AUTOHALER is contraindicated in patients with a history of hypersensitivity to pirbuterol or any of its ingredients.

### WARNINGS

**Cardiovascular:** MAXAIR AUTOHALER, like other inhaled 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 MAXAIR AUTOHALER at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Therefore, MAXAIR AUTOHALER, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

**Paradoxical Bronchospasm:** MAXAIR AUTOHALER can produce paradoxical bronchospasm, which can be life threatening. If paradoxical bronchospasm occurs, MAXAIR AUTOHALER 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.

**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.

**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 MAXAIR AUTOHALER 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.

### PRECAUTIONS

**General:** Since pirbuterol is a sympathomimetic amine, it should be used with caution in patients with cardiovascular disorders, including ischemic heart disease, hypertension, or cardiac arrhythmias, in patients with hyperthyroidism or diabetes mellitus, and in patients who are unusually responsive to sympathomimetic amines or who have convulsive disorders. Significant changes in systolic and diastolic blood pressure could be expected to occur in some patients after use of any beta adrenergic aerosol bronchodilator.

Beta adrenergic agonist medications 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 MAXAIR AUTOHALER should last up to five hours or longer. MAXAIR AUTOHALER should not be used more frequently than recommended. Do not increase the dose or frequency of MAXAIR AUTOHALER without consulting your physician. If you find that treatment with MAXAIR AUTOHALER becomes less effective for symptomatic relief, or 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 MAXAIR AUTOHALER, 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 MAXAIR AUTOHALER. Effective and safe use includes an understanding of the way the medication should be administered. As with all aerosol medications, it is recommended to prime (test) MAXAIR AUTOHALER before using for the first time. MAXAIR AUTOHALER should also be primed if it has not been used in 48 hours. As described in the priming procedure, use the test fire slide to release two priming sprays into the air away from yourself and other people. (See "Patient's Instructions For Use" portion of this package insert.) The MAXAIR AUTOHALER actuator should not be used with any other inhalation aerosol canister. In addition, canisters for use with MAXAIR AUTOHALER should not be utilized with any other actuator.

**Drug Interactions:** Other short-acting beta adrenergic aerosol bronchodilators should not be used concomitantly with MAXAIR AUTOHALER because they may have additive effects.

**Monoamine Oxidase Inhibitors or Tricyclic Antidepressants:** Pirbuterol 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 pirbuterol 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 MAXAIR AUTOHALER, 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.

**Carcinogenesis, Mutagenesis and Impairment of Fertility:** In a 2-year study in Sprague-Dawley rats, pirbuterol hydrochloride administered at dietary doses of 1.0, 3.0, and 10 mg/kg (approximately 3, 10, and 35 times the maximum recommended daily inhalation dose for adults and children on a mg/m<sup>2</sup> basis) showed no evidence of carcinogenicity. In an 18-month study in mice at dietary doses of 1.0, 3.0, and 10 mg/kg (approximately 2, 5, and 15 times the maximum recommended daily inhalation dose for adults and children on a mg/m<sup>2</sup> basis) no evidence of tumorigenicity was seen. Reproduction studies in rats administered pirbuterol hydrochloride at

oral doses of 1, 3, and 10 mg/kg (approximately 3, 10, and 35 times the maximum recommended daily inhalation dose for adults on a mg/m<sup>2</sup> basis) revealed no evidence of impaired fertility.

Pirbuterol dihydrochloride showed no evidence of mutagenicity in *in vitro* assays and host-mediated microbial (Ames) assays for point mutations and *in vivo* tests for somatic or germ cell effects following acute and subchronic treatment in mice (cytogeneticity assays).

**Teratogenic Effects – Pregnancy Category C:** Pirbuterol was not teratogenic in rats administered oral doses of 30, 100, and 300 mg/kg (approximately 100, 340, and 1000 times the maximum recommended daily inhalation dose for adults on a mg/m<sup>2</sup> basis). Pirbuterol was not teratogenic in rabbits administered oral doses of 30 and 100 mg/kg (approximately 200 and 680 times the maximum recommended inhalation dose for adults on a mg/m<sup>2</sup> basis). However, pirbuterol at an oral dose of 300 mg/kg (approximately 2000 times the maximum recommended daily inhalation dose in adults on a mg/m<sup>2</sup> basis) caused abortions and fetal death.

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

**Labor and Delivery:** Because of the potential for beta-agonist interference with uterine contractility, use of MAXAIR AUTOHALER for relief of bronchospasm during labor should be restricted to those patients in whom the benefits clearly outweigh the risk.

**Nursing Mothers:** It is not known whether pirbuterol is excreted in human milk. Therefore, MAXAIR AUTOHALER should be used during nursing only if the potential benefit justifies the possible risk to the newborn.

**Pediatric Use:** MAXAIR AUTOHALER is not recommended for patients under the age of 12 years because of insufficient clinical data to establish safety and effectiveness.

#### ADVERSE REACTIONS

The following rates of adverse reactions to pirbuterol are based on single- and multiple-dose clinical trials involving 761 patients, 400 of whom received multiple doses (mean duration of treatment was 2.5 months and maximum was 19 months).

The following were the adverse reactions reported more frequently than 1 in 100 patients:

**CNS:** nervousness (6.9%), tremor (6.0%), headache (2.0%), dizziness (1.2%).

**Cardiovascular:** palpitations (1.7%), tachycardia (1.2%).

**Respiratory:** cough (1.2%).

**Gastrointestinal:** nausea (1.7%).

The following adverse reactions occurred less frequently than 1 in 100 patients and there may be a causal relationship with pirbuterol:

**CNS:** depression, anxiety, confusion, insomnia, weakness, hyperkinesia, syncope.

**Cardiovascular:** hypotension, skipped beats, chest pain.

**Gastrointestinal:** dry mouth, glossitis, abdominal pain/cramps, anorexia, diarrhea, stomatitis, nausea and vomiting.

**Ear, Nose and Throat:** smell/taste changes, sore throat.

**Dermatological:** rash, pruritus.

**Other:** numbness in extremities, alopecia, bruising, fatigue, edema, weight gain, flushing.

Other adverse reactions were reported with a frequency of less than 1 in 100 patients but a causal relationship between pirbuterol and the reaction could not be determined: migraine, productive cough, wheezing, and dermatitis.

The following rates of adverse reactions during three-month controlled clinical trials involving 310 patients are noted. The table does not include mild reactions.

#### PERCENT OF PATIENTS WITH MODERATE TO SEVERE ADVERSE REACTIONS

Reaction	Pirbuterol N=157	Metaproterenol N=153
<b>Central Nervous System</b>		
tremors	1.3%	3.3%
nervousness	4.5%	2.6%
headache	1.3%	2.0%
weakness	.0%	1.3%
drowsiness	.0%	0.7%
dizziness	0.6%	.0%
<b>Cardiovascular</b>		
palpitations	1.3%	1.3%
tachycardia	1.3%	2.0%
<b>Respiratory</b>		
chest pain/tightness	1.3%	.0%
cough	.0%	0.7%
<b>Gastrointestinal</b>		
nausea	1.3%	2.0%
diarrhea	1.3%	0.7%
dry mouth	1.3%	1.3%
vomiting	.0%	0.7%
<b>Dermatological</b>		
skin reaction	.0%	0.7%
rash	.0%	1.3%
<b>Other</b>		
bruising	0.6%	.0%
smell/taste change	0.6%	.0%
backache	.0%	0.7%
fatigue	.0%	0.7%
hoarseness	.0%	0.7%
nasal congestion	.0%	0.7%

**Electrocardiograms:** Electrocardiograms, obtained during a randomized, double-blind, cross-over study in 57 patients, showed no observations or findings considered clinically significant, or related to drug administration. Most electrocardiographic observations, obtained during a randomized, double-blind, cross-over study in 40 patients, were judged not clinically significant or related to drug administration. One patient was noted to have some changes on the one hour postdose electrocardiogram consisting of ST and T wave abnormality suggesting possible inferior ischemia. This abnormality was not observed on the predose or the six hours postdose ECG. A treadmill was subsequently performed and all the findings were normal.

#### OVERDOSAGE

The expected symptoms with overdosage are those of excessive beta-stimulation and/or 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 medication, cardiac arrest and even death may be associated with abuse of MAXAIR AUTOHALER.

Treatment consists of discontinuation of pirbuterol 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.

The oral median lethal dose of pirbuterol dihydrochloride in mice and rats is greater than 2000 mg/kg (approximately 3400 and 6800 times the maximum recommended daily inhalation dose for adults on a mg/m<sup>2</sup> basis).

#### DOSAGE AND ADMINISTRATION

The usual dose for adults and children 12 years and older is two inhalations (400 mcg) repeated every 4-6 hours. One inhalation (200 mcg) repeated every 4-6 hours may be sufficient for some patients.

A total daily dose of 12 inhalations should not be exceeded.

If a previously effective dosage regimen fails to provide the usual relief, medical advice should be sought immediately as this is often a sign of seriously worsening asthma which would require reassessment of the therapy.

#### HOW SUPPLIED

MAXAIR AUTOHALER, box of one, is supplied in a pressurized aluminum canister with a light blue plastic breath-activated actuator and a light blue mouthpiece cover. DO NOT USE WITH OTHER CANISTERS OR MOUTHPIECES. Each actuation delivers 253 mcg of pirbuterol (as pirbuterol acetate) from the valve and 200 mcg of pirbuterol (as pirbuterol acetate) from the mouthpiece.

Canister net content weight 14.0 g, 400 inhalations (NDC 29336-815-21) and canister net content weight 2.8 g, 80 inhalations (Sample Pack: NDC 29336-815-08).

The correct amount of medication in each canister cannot be assured after 80 actuations from the 2.8 g canister and 400 actuations from the 14.0 g canister, even though the canister is not completely empty. The canister should be discarded when the labeled numbers of actuations have been used.

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

**WARNING:** Contains trichloromonofluoromethane and dichlorodifluoromethane, substances which harm public health and 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.

#### Rx only

Store between 15° and 30°C (59° to 86°F). Failure to use this 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.

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

The light blue plastic actuator supplied with MAXAIR AUTOHALER should not be used with any other product canisters, and actuators from other product should not be used with MAXAIR AUTOHALER canister.

Distributed by:  
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