

# Metaproterenol Sulfate Inhalation Solution USP

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### Prescribing Information

#### Rx Only

#### Metaproterenol Sulfate Inhalation Solution USP 0.4% and 0.6%

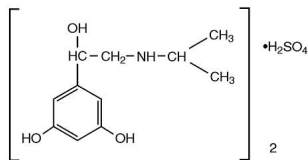
#### Unit-Dose Ampule Bronchodilator

#### STERILE - FOR INHALATION USE ONLY

#### DESCRIPTION

Metaproterenol Sulfate Inhalation Solution USP is a bronchodilator administered by oral inhalation with the aid of an intermittent positive pressure breathing apparatus (IPPB). It contains metaproterenol sulfate USP 0.4% or 0.6% in a sterile pH adjusted aqueous solution with edetate disodium and sodium chloride. Sulfuric acid may be added to adjust pH if necessary.

Chemically, metaproterenol sulfate is ( $\pm$ )-3,5-Dihydroxy- $\alpha$ -[(isopropylamino) methyl]benzyl alcohol sulfate, a white crystalline, racemic mixture of two optically active isomers. It differs from isoproterenol hydrochloride by having two hydroxyl groups attached at the meta positions on the benzene ring rather than one at the meta and one at the para position.



metaproterenol sulfate

(C<sub>11</sub>H<sub>17</sub>NO<sub>3</sub>)<sub>2</sub>•H<sub>2</sub>SO<sub>4</sub>  
Mol. Wt. 520.60

#### CLINICAL PHARMACOLOGY

Metaproterenol sulfate is a potent beta-adrenergic stimulator with a rapid onset of action. It is postulated that beta-adrenergic stimulants produce many of their pharmacological effects by activation of adenyl cyclase, the enzyme which catalyzes the conversion of adenosine triphosphate to cyclic adenosine monophosphate.

Absorption, biotransformation and excretion studies following administration by inhalation have not been performed. Following oral administration in humans, an average of 40% of the drug is absorbed; it is not metabolized by catechol-O-methyltransferase but is excreted primarily as glucuronic acid conjugates.

#### INDICATIONS AND USAGE

Metaproterenol sulfate inhalation solution is indicated as a bronchodilator for bronchial asthma and for reversible bronchospasm which may occur in association with bronchitis and emphysema.

Following controlled single dose studies by an intermittent positive pressure breathing apparatus (IPPB) and by hand bulb nebulizers, significant improvement (15% or greater increase in FEV<sub>1</sub>) occurred within 5 to 30 minutes and persisted for periods varying from 2 to 6 hours.

In these studies, the longer duration of effect occurred in the studies in which the drug was administered by IPPB, i.e. 6 hours versus 2 to 3 hours when administered by hand bulb nebulizer. In these studies the doses used were 0.3 mL by IPPB and 10 inhalations by hand bulb nebulizer.

In controlled repetitive dosing studies by IPPB and by hand bulb nebulizer the onset of effect occurred within 5 to 30 minutes and duration ranged from 4 to 6 hours. In these studies the doses used were 0.3 mL b.i.d. or t.i.d. when given by IPPB, and 10 inhalations q.i.d. (no more

often than q4h) when given by hand bulb nebulizer. As in the single dose studies, effectiveness was measured as a sustained increase in FEV<sub>1</sub> of 15% or greater. In these repetitive dosing studies there was no apparent difference in duration between the two methods of delivery.

Clinical studies were conducted in which the effectiveness of metaproterenol sulfate inhalation solution was evaluated by comparison with that of isoproterenol hydrochloride over periods of two to three months. Both drugs continued to produce significant improvement in pulmonary function throughout this period of treatment.

#### CONTRAINDICATIONS

Use in patients with cardiac arrhythmias associated with tachycardia is contraindicated.

Although rare, immediate hypersensitivity reactions can occur. Therefore, metaproterenol sulfate inhalation solution, 0.4% or 0.6% is contraindicated in patients with a history of hypersensitivity to any of its components.

#### WARNINGS

Excessive use of adrenergic aerosols is potentially dangerous. Fatalities have been reported following excessive use of metaproterenol sulfate as with other sympathomimetic inhalation preparations, and the exact cause is unknown. Cardiac arrest was noted in several cases.

Paradoxical bronchoconstriction with repeated excessive administration has been reported with sympathomimetic agents.

Patients should be advised to contact their physician in the event that they do not respond to their usual dose of sympathomimetic amine aerosol.

#### PRECAUTIONS

Because metaproterenol sulfate inhalation solution is a sympathomimetic drug, it should be used with great caution in patients with hypertension, coronary artery disease, congestive heart failure, hyperthyroidism or diabetes, or when there is sensitivity to sympathomimetic amines.

**Information for Patients:** Extreme care must be exercised with respect to the administration of additional sympathomimetic agents. A sufficient interval of time should elapse prior to administration of another sympathomimetic agent.

**Carcinogenesis:** Long-term studies in mice and rats to evaluate the oral carcinogenic potential of metaproterenol sulfate have not been completed.

Studies of metaproterenol sulfate have not been conducted to determine mutagenic potential or effect on fertility.

**Pregnancy:** *Teratogenic Effects, Pregnancy Category C.* Metaproterenol sulfate has been shown to be teratogenic and embryocidal in rabbits when given orally in doses 620 times the human inhalation dose. There are no adequate and well-controlled studies in pregnant women. Metaproterenol sulfate inhalation solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Oral reproduction studies in mice, rats and rabbits showed no teratogenic or embryocidal effects at 50 mg/kg corresponding to 310 times the human inhalation dose. Teratogenic effects in the rabbit included skeletal abnormalities and hydrocephalus with bone separation.

**Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised

when metaproterenol sulfate inhalation solution is administered to a nursing woman.

**Pediatric Use:** Safety and effectiveness in the pediatric population below the age of 12 have not been established.

#### ADVERSE REACTIONS

Adverse reactions are similar to those noted with other sympathomimetic agents.

The most frequent adverse reactions to metaproterenol sulfate are nervousness and tachycardia which occur in about 1 in 7 patients, tremor which occurs in about 1 in 20 patients and nausea which occurs in about 1 in 50 patients. Less frequent adverse reactions are hypertension, palpitations, vomiting and bad taste which occur in approximately 1 in 300 patients.

#### OVERDOSAGE

The symptoms of overdosage are those of excessive beta-adrenergic stimulation listed under ADVERSE REACTIONS. These reactions usually do not require treatment other than reduction of dosage and/or frequency of administration.

#### DOSAGE AND ADMINISTRATION

Metaproterenol sulfate inhalation solution unit-dose ampule is administered by oral inhalation using an IPPB device. The usual adult dose is one plastic ampule per nebulization treatment. Each ampule of metaproterenol sulfate inhalation solution 0.4% is equivalent to 0.2 mL metaproterenol sulfate inhalation solution 5% diluted to 2.5 mL with normal saline; each ampule of metaproterenol sulfate inhalation solution 0.6% is equivalent to 0.3 mL metaproterenol sulfate inhalation solution 5% diluted to 2.5 mL with normal saline.

Usually, treatment need not be repeated more often than every four hours to relieve acute attacks of bronchospasm. As part of a total treatment program in chronic bronchospastic pulmonary diseases, metaproterenol sulfate inhalation solution may be administered three to four times a day.

As with all medications, the physician should begin therapy with the lowest effective dose and then titrate the dosage according to the individual patient's requirements.

Metaproterenol sulfate inhalation solution is not recommended for use in children under 12 years of age.

#### HOW SUPPLIED

Metaproterenol sulfate inhalation solution 0.4% is supplied as a clear, colorless solution in 2.5 mL plastic ampules, with 25 plastic ampules per carton (5 ampules per foil pouch). NDC 60505-0807-1.

Metaproterenol sulfate inhalation solution 0.6% is supplied as a clear, colorless solution in 2.5 mL plastic ampules, with 25 plastic ampules per carton (5 ampules per foil pouch). NDC 60505-0808-1.

Each plastic ampule is made from low density polyethylene resin.

**Store below 25°C (77°F). Protect from light. Store unused plastic ampules in the foil pouch. Do not use the solution if it is pinkish or darker than slightly yellow or contains a precipitate.**

**Manufactured by:**  
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Canada L4C 5H2

Manufactured for:  
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