ASTHALIN Rotacaps (Salbutamol sulphate)

Composition

Each capsule contains:

Salbutamol Sulphate IP equivalent to Salbutamol IP .....200 mcg

Excipients .....q.s

Dosage Form

Dry powder for inhalation

Pharmacology

Pharmacodynamics

Salbutamol is a selective beta$_2$-adrenoceptor agonist. At therapeutic doses, it acts on the beta$_2$-adrenoceptors of bronchial smooth muscle, with little or no action on the beta$_1$-adrenoceptors of cardiac muscle. Salbutamol provides short-acting (4-6 hours) bronchodilatation with a fast onset (within 5 minutes) in reversible airways obstruction.

Pharmacokinetics

Salbutamol administered intravenously has a half-life of 4-6 hours, and is cleared partly renally and partly by metabolism to the inactive 4'-O-sulphate (phenolic sulphate), which is also excreted primarily in the urine. The faeces are a minor route of excretion.

After administration by the inhaled route, between 10% and 20% of the dose reaches the lower airways. The remainder is retained in the delivery system or is deposited in the oropharynx from where it is swallowed. The fraction deposited in the airways is absorbed into the pulmonary tissues and circulated, but is not metabolized by the lungs. On reaching the systemic circulation, it becomes accessible to hepatic metabolism and is excreted, primarily in the urine, as unchanged drug and as phenolic sulphate.

The swallowed portion of an inhaled dose is absorbed from the gastrointestinal tract and undergoes considerable first-pass metabolism to phenolic sulphate. Both unchanged drug and conjugate are excreted primarily in the urine. Most of a dose of salbutamol given intravenously, orally, or by inhalation is excreted within 72 hours. Salbutamol is bound to plasma proteins to the extent of 10%.

Indications

Bronchospasm

ASTHALIN Rotacaps are indicated for the treatment or prevention of bronchospasm in patients 4 years of age and older with reversible obstructive airway disease.

Exercise-Induced Bronchospasm

ASTHALIN Rotacaps are indicated for the prevention of exercise induced bronchospasm in patients 4 years of age and older.

Dosage and Administration

ASTHALIN Rotacaps are for inhalation use, only through the **Cipla Rotahaler/Revolizer.** **ASTHALIN Rotacaps** must not be swallowed.

Adults (Including the Elderly)

For relief of acute episodes of bronchospasm:

1 Rotacap as a single dose

To prevent allergen- or exercise-induced bronchospasm:

1 Rotacap, 15 minutes prior to exercise or exposure to allergen

For chronic therapy, 200 micrograms four times a day

The maximum dose up to 800 mcg in 24 hours

Children

For relief of acute episodes of bronchospasm:

1 Rotacap as a single dose

To prevent allergen- or exercise-induced bronchospasm:

1 Rotacap, 15 minutes prior to exercise or exposure to allergen

For chronic therapy, children aged 4 to 11 years 200 micrograms four times a day.

The maximum dose up to 800 mcg in 24 hours.

Contraindications

Hypersensitivity to any of the components

- Rare cases of hypersensitivity reactions including urticaria, angioedema and rash have been reported after the use of salbutamol.
- Although intravenous salbutamol, and occasionally salbutamol tablets, are used in the management of premature labour uncomplicated by conditions such as placenta praevia, ante-partum haemorrhage, or toxaemia of pregnancy, inhaled salbutamol preparations are not appropriate for managing premature labour. Salbutamol preparations should not be used for threatened abortion.

Warnings and Precautions

Paradoxical Bronchospasm

Inhaled salbutamol sulphate can produce paradoxical bronchospasm, which may be life-threatening. If paradoxical bronchospasm occurs, **ASTHALIN Rotacaps** should be discontinued immediately and alternative therapy instituted.

Cardiovascular Effects

Salbutamol, like all other beta$_2$-adrenergic agonists, can produce clinically significant cardiovascular effects in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of salbutamol 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, salbutamol, 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 **ASTHALIN Rotacaps** than usual, this may be a marker of destabilization of asthma and requires re-evaluation of the patient and treatment regimen, with 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, to the therapeutic regimen.

Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions may occur after administration of salbutamol sulphate inhalation aerosol, as demonstrated by cases of urticaria, angio-oedema, rash, bronchospasm, hypotension and anaphylaxis. Discontinue **ASTHALIN Rotacaps** if immediate hypersensitivity reactions occur.

Do Not Exceed Recommended Dose

Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma. The exact cause of death is unknown, but cardiac arrest following an unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is suspected.

Coexisting conditions

Salbutamol, like other sympathomimetic amines, should be used with caution in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus and in patients who are unusually responsive to sympathomimetic amines. Salbutamol should be administered cautiously to patients with thyrotoxicosis. Large doses of intravenous salbutamol have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

Hypokalemia

As with other beta-agonists, salbutamol 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.

Drug Interactions

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

Beta-Adrenergic Receptor Blocking Agents: Beta-blockers not only block the pulmonary effect of beta-agonists, such as **ASTHALIN Rotacaps**, but may also produce severe bronchospasm in patients with asthma. Therefore, patients with asthma should not normally be treated with beta-blockers. **ASTHALIN Rotacaps** and non-selective beta-blocking drugs such as propranolol, should not usually be prescribed together. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to use beta-adrenergic blocking agents in patients with asthma. In this setting, cardioselective beta-blockers should be considered, although they should be administered with caution.

Non-Potassium-Sparing 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 relevance of these effects is not known, caution is advised in the co-administration of beta-agonists with non-potassium-sparing diuretics. Consider monitoring potassium levels.

Particular caution is advised in acute severe asthma as this effect may be potentiated by con-comitant treatment with xanthine derivatives, steroids, digoxin, diuretics, and by hypoxia. It is recommended that serum potassium levels be monitored in such situations.

Digoxin: Mean decreases of 16% to 22% in serum digoxin levels were demonstrated after single dose intravenous and oral administration of salbutamol, respectively, to normal volunteers who had received digoxin for 10 days. The clinical relevance of these findings for patients with obstructive airway disease who are receiving inhaled salbutamol 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 salbutamol.

Monoamine Oxidase Inhibitors or Tricyclic Antidepressants: **ASTHALIN Rotacaps** should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants or within 2 weeks discontinuation of such agents, because the action of salbutamol on the vascular system may be potentiated.

Pregnancy

Pregnancy Category C

Administration of **ASTHALIN Rotacaps** during pregnancy should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus. As with the majority of drugs, there is little published evidence of the safety of salbutamol in the early stages of human pregnancy, but in animal studies there was evidence of some harmful effects on the fetus at very high dose

levels.

There are no well-controlled human trials that have investigated effects of salbutamol on preterm labor or labor at term. Because of the potential for beta-agonist interference with uterine contractility, use of **ASTHALIN Rotacaps** during labor should be restricted to those patients in whom the benefits clearly outweigh the risk.

Lactation
As salbutamol is probably secreted in breast milk, its use in nursing mothers requires careful consideration. It is not known whether salbutamol has a harmful effect on the neonate, and so its use should be restricted to situations where it is felt that the expected benefit to the mother is likely to outweigh any potential risk to the neonate.

Pediatric Patients

Results from the 2-week pediatric clinical study in patients with asthma 4 to 11 years of age showed that the adverse reaction profile was similar to that of the adolescent and adult population. These adverse reactions included upper respiratory tract infection, nasopharyngitis, pyrexia and tachycardia. The safety and effectiveness of **ASTHALIN** Inhaler in children under 4 years of age has not been demonstrated.

Geriatric Patients

Clinical trials of salbutamol did not include sufficient numbers of subjects aged 65 years and older to determine whether older subjects respond differently than younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Undesirable Effects

Use of **ASTHALIN Rotacaps** may be associated with paradoxical bronchospasm, cardiovascular effects, immediate hypersensitivity reactions and hypokalemia. Other rare undesirable effects included hypotension and collapse, mouth and throat irritation, muscle cramps and peripheral vasodilatation. Myocardial infarction was reported as an unknown undesirable effect with salbutamol. Common side effects with salbutamol included tremor and headache.

Clinical Trials Experience

Adults and Adolescents 12 years of age and older-

The two 12-week, randomized, double blind studies in 610 adolescent and adult patients with asthma that compared salbutamol with placebo showed common (3% or greater reported) adverse reactions – ear, nose and throat irritation, upper respiratory inflammation, lower respiratory (viral respiratory infections, cough) and musculoskeletal pain.

Adverse reactions reported by less than 3% of the adolescents and adult patients include diarrhea, laryngitis, oropharyngeal edema, cough, lung disorders, tachycardia, extrasystoles, palpitation and dizziness.

Post marketing Experience

Paradoxical bronchospasm, hoarseness, arrhythmias (including atrial fibrillation, supraventricular tachycardia, and extrasystoles), and hypersensitivity reactions (including urticaria, angioedema, rash) have been reported.

In addition, salbutamol like other sympathomimetic agents, can cause adverse reactions such as hypokalemia, hypertension, peripheral vasodilation, angina, tremor, central nervous system stimulation, hyperactivity, sleeplessness, headache, muscle cramps, drying or irritation of the oropharynx, and metabolic acidosis.

If you experience any side-effects, talk to your doctor or pharmacist or write to drugsafety@cipla.com. You can also report side effects directly via the national pharmacovigilance program of India by calling on 1800 180 3024.

By reporting side-effects, you can help provide more information on the safety of this product.

Overdosage

The expected symptoms of overdosage are those of excessive beta-adrenergic stimulation, and/or occurrence or exaggeration of any of the signs and symptoms of beta-adrenergic stimulation viz., seizures, angina, hypertension or hypotension, tachycardia (with rates up to 200 beats/min), arrhythmias, nervousness, headache, tremor, hyperactivity, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, sleeplessness, hyperglycemia, hypokalemia and metabolic acidosis (serum potassium levels should be monitored). Cardiac arrest and, even, death is associated with the abuse of **ASTHALIN Rotacaps**.

Treatment consists of discontinuation of **ASTHALIN Rotacaps** together with appropriate symptomatic therapy. The preferred antidote for overdosage with salbutamol is a cardioselective beta-blocking agent, but beta-blocking drugs should be used with caution in patients with a history of bronchospasm.

If hypokalemia occurs, potassium replacement via the oral route should be given. In patients with severe hypokalemia, intravenous replacement may be necessary. There is insufficient evidence to determine if dialysis is beneficial for overdosage of salbutamol. Lactic acidosis has been reported in association with high therapeutic doses as well as overdoses of short-acting beta-agonist therapy, therefore monitoring for elevated serum lactate and consequent metabolic acidosis (particularly if there is persistence or worsening of tachypnea despite resolution of other signs of bronchospasm such as wheezing) may be indicated in the setting of overdose.

Packaging Information

ASTHALIN Rotacaps .....30 Rotacaps

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