LEVOLIN Respules (Levosalbutamol sulphate)

Composition

LEVOLIN Respules 0.31 mg
Each 2.5 ml contains:
Levosalbutamol Sulphate
Equivalent to Levosalbutamol ....... 0.31 mg
In normal saline solution .............. q.s.

LEVOLIN Respules 0.63 mg
Each 2.5 ml contains:
Levosalbutamol Sulphate
Equivalent to Levosalbutamol ....... 0.63 mg
In normal saline solution .............. q.s.

LEVOLIN Respules 1.25 mg
Each 2.5 ml contains:
Levosalbutamol Sulphate
Equivalent to Levosalbutamol ....... 1.25 mg
In normal saline solution .............. q.s.

Dosage Form

Solution for inhalation via nebulizer

Description

Leyesalbutamol is the purified enantiomer of racemic Salbutamol (both R and S) that has a 100-fold greater affinity for the β2-receptor as compared to (S)-salbutamol.

Pharmacology

Pharmacodynamics

LEVOLIN Respules contain a unit dose each of sterile, clear, colourless, preservative-free solution of the sulphate salt of levosalbutamol. Levosalbutamol is a single isomer β₂-agonist that differs from racemic salbutamol by the elimination of (S)-salbutamol. Levosalbutamol is an effective bronchodilator whose primary mechanism of action is unimpeded by (S)-salbutamol. Therefore, it can be used in doses that are half that of racemic salbutamol.

Activation of β₂-adrenergic receptors on airway smooth muscle leads to the activation of adenylyl cyclase and to an increase in the intracellular concentration of cyclic-3', 5'-adenosine monophosphate (cyclic AMP). This increase in cyclic AMP leads to the activation of protein kinase A, which inhibits the phosphorylation of myosin and lowers intracellular...
ionic calcium concentrations, resulting in relaxation. Levosalbutamol relaxes the smooth muscles of all airways, from the trachea to the terminal bronchioles. Levosalbutamol acts as a functional antagonist that relaxes the airway irrespective of the spasmogen involved, thereby protecting against all bronchoconstrictor challenges. Increased cyclic AMP concentrations are also associated with the inhibition of release of mediators from mast cells in the airway.

While it is recognized that beta₂-adrenergic receptors are the predominant receptors on bronchial smooth muscle, data indicate that there is a population of beta₂-receptors in the human heart that comprise between 10-50% of cardiac beta-adrenergic receptors. The precise function of these receptors has not been established. However, all beta-adrenergic agonist drugs can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, symptoms, and/or electrocardiographic (ECG) changes.

Pharmacokinetics

Absorption and Distribution (Adults and Adolescents)
The inhalation pharmacokinetics of levosalbutamol inhalation solution were investigated in a randomized crossover study in 30 healthy adults, following administration of a single dose of 1.25 mg and a cumulative dose of 5 mg of levosalbutamol inhalation solution, and a single dose of 2.5 mg and a cumulative dose of 10 mg of racemic salbutamol inhalation solution by nebulization, using the nebulizer with a compressor.

Following administration of a single 1.25 mg dose of levosalbutamol inhalation solution, exposure to (R)-salbutamol was approximately 2-fold higher than following administration of a single 2.5 mg dose of racemic salbutamol inhalation solution (AUC of 1.7 ng·hr/mL) (see table below).

Following administration of a cumulative 5 mg dose of levosalbutamol inhalation solution (1.25 mg given every 30 minutes for a total of four doses) or a cumulative 10 mg dose of racemic salbutamol inhalation solution (2.5 mg given every 30 minutes for a total of four doses), C_{max} and AUC of (R)-salbutamol were comparable.

<table>
<thead>
<tr>
<th></th>
<th>Single Dose</th>
<th>Cumulative Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Levosalbutamol 1.25 mg</td>
<td>Racemic Salbutamol 2.5 mg</td>
</tr>
<tr>
<td>C_{max} (ng/mL) (R)-salbutamol</td>
<td>1.1 (0.45)</td>
<td>0.8 (0.41) **</td>
</tr>
<tr>
<td>t_{max} (h) (gamma) (R)-salbutamol</td>
<td>0.2 (0.17, 0.37)</td>
<td>0.2 (0.17, 1.50)</td>
</tr>
<tr>
<td>AUC (ng·h/mL) (R)-salbutamol</td>
<td>3.3 (1.58)</td>
<td>1.7 (0.99) **</td>
</tr>
<tr>
<td>T_{1/2} (h) (R)-salbutamol</td>
<td>3.3 (2.48)</td>
<td>1.5 (0.61)</td>
</tr>
</tbody>
</table>

Pharmacokinetics (Children 6-11 Years Old)
The pharmacokinetic parameters of (R)- and (S)-salbutamol in children with asthma were obtained using population pharmacokinetics analysis. These data are presented in Table 2. For comparison, adult data obtained by conventional pharmacokinetics analysis from a different study also are presented in Table below.

In children, AUC and C_{max} of (R)-salbutamol following administration of 0.63 mg levosalbutamol inhalation solution were comparable to those following administration of 1.25 mg Racemic Salbutamol inhalation solution.

When the same dose of 0.63 mg of levosalbutamol was given to children and adults, the predicted C_{max} of (R)-salbutamol
in children was similar to that in adults (0.52 versus 0.56 ng/mL), while predicted AUC in children (2.55 ng·hr/mL) was about 1.5-fold higher than that in adults (1.65 ng·hr/mL). These data support lower doses for children aged 6–11 years old, compared with the adult doses.

### (R)-Salbutamol Exposure in Adults, Adolescents, and Paediatric Subjects

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Children (6-11 years old)</th>
<th>Adults and Adolescents</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Levo salbutamol 0.31 mg</td>
<td>Levo salbutamol 0.63 mg</td>
</tr>
<tr>
<td></td>
<td>Levo salbutamol 0.63 mg</td>
<td>Racemic Salbutamol 1.25 mg</td>
</tr>
<tr>
<td></td>
<td>Racemic Salbutamol 2.5 mg</td>
<td></td>
</tr>
<tr>
<td>AUC0-(infinity) (ng·hr/mL)</td>
<td>1.36</td>
<td>2.55</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>0.303</td>
<td>0.521</td>
</tr>
</tbody>
</table>

*The values are predicted by assuming linear pharmacokinetics.
*The data obtained from Table 1.
*Area under the plasma concentration curve from time 0 to infinity.
*Maximum plasma concentration

### Metabolism and Elimination

Information available in published literature suggests that the primary enzyme responsible for the metabolism of salbutamol enantiomers in humans is SULT1A3 (sulphotransferase). When racemic salbutamol was administered either intravenously or via inhalation after oral charcoal administration, there was a 3- to 4-fold difference in the AUCs between the (R)- and (S)-salbutamol enantiomers, with (S)-salbutamol concentrations being consistently higher. However, after either inhalation or oral administration without charcoal pre-treatment, the differences were 8- to 24-fold, suggesting that (R)-salbutamol is preferentially metabolized in the gastrointestinal tract, presumably by SULT1A3.

The primary route of elimination of salbutamol enantiomers is through renal excretion (80-100%) of either the parent compound or the primary metabolite. Less than 20% of the drug is detected in the faeces. Following intravenous administration of racemic salbutamol, between 25-46% of the (R)-salbutamol fraction of the dose was excreted as unchanged (R)-salbutamol in the urine.

### Indications

LEVOLIN Respules are indicated for the treatment or prevention of bronchospasm in adults, adolescents, and children (6-11 years old) with reversible obstructive airway disease.

### Dosage And Administration

**Children (6-11 years old)**

*LEVOLIN Respules 0.31 mg*

Recommended for use only in children.

0.31 mg (2.5 ml), three times a day.

Routine dosing should not exceed 0.63 mg three times a day.
Adults and Adolescents (≥ 12 years)

**LEVOLIN Respules 0.63 mg**
0.63 mg (2.5 ml), three times a day, every 6-8 hours by nebulization.

**LEVOLIN Respules 1.25 mg**
In patients with severe asthma who do not respond adequately to a dose of 0.63 mg, 1.25 mg (2.5 ml) three times a day can be given.

Patients receiving higher dose of LEVOLIN Respules should be monitored closely for adverse systemic effects.

### Contraindications

Hypersensitivity to any of the components of the formulation.

### Warnings And Precautions

LEVOLIN Respules, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, hypertension, and cardiac arrhythmias; 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 in individual patients and could be expected to occur in some patients after the use of any beta-adrenergic bronchodilator.

Large doses of intravenous racemic salbutamol have been reported to aggravate pre-existing diabetes mellitus and ketoacidosis. As with other beta-adrenergic agonist medications, LEVOLIN Respules 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.

### Paradoxical Bronchospasm

Like other inhaled beta-adrenergic agonists, LEVOLIN Respules can produce paradoxical bronchospasm, which may be life-threatening. If paradoxical bronchospasm occurs, LEVOLIN Respules 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.

### 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 LEVOLIN Respules 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 a beta-adrenergic agonist 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.

### Cardiovascular Effects

LEVOLIN Respules, like other beta-adrenergic agonists, can produce clinically significant cardiovascular effects in some patients, as measured by heart rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of LEVOLIN Respules 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, levosalbutamol sulphate inhalation solution, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

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.

Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions may occur after administration of racemic salbutamol, as demonstrated by rare cases of urticaria, angio-oedema, rash, bronchospasm, anaphylaxis, and oropharyngeal oedema. The potential for hypersensitivity must be considered in the clinical evaluation of patients who experience immediate hypersensitivity reactions while receiving LEVOLIN Respules.

Coexisting Conditions

LEVOLIN Respules, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, hypertension, and cardiac arrhythmias; in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus; and in patients who are unusually responsive to sympathomimetic amines. Clinically signicant changes in systolic and diastolic blood pressure have been seen in individual patients and could be expected to occur in some patients after the use of any betaadrenergic bronchodilator. Changes in blood glucose may occur. Large doses of intravenous racemic albuterol have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

Drug Interactions

Other short-acting sympathomimetic bronchodilators or epinephrine should be used with caution with levosalbutamol. If additional adrenergic drugs are to be administered by any route, they should be used with caution to avoid deleterious cardiovascular effects.

Beta-Blockers

Beta-adrenergic receptor blocking agents not only block the pulmonary effect of beta-agonists such as levosalbutamol, but may also produce severe bronchospasm in asthmatic patients. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, use of beta-adrenergic blocking agents could be considered, although they should be administered with caution.

Diuretics

The ECG changes and/or hypokalaemia 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. Hence, caution is advised in the co-administration of beta-agonists with non-potassium-sparing diuretics.

Digoxin

Mean decreases of 16% and 22% in serum digoxin levels were demonstrated after single-dose intravenous and oral administration of racemic salbutamol to normal volunteers who had received digoxin for 10 days; hence, it is advisable to carefully evaluate the serum digoxin levels in patients who are currently receiving digoxin and levosalbutamol.

Monoamine Oxidase Inhibitors or Tricyclic Antidepressants:

LEVOLIN Respules 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
levosalbutamol on the vascular system may be potentiated.

Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of LEVOLIN Respules has not been evaluated.

Renal Impairment

The effect of renal impairment on the pharmacokinetics of racemic salbutamol was evaluated in 5 subjects with creatinine clearance of 7–53 mL/min, and the results were compared with those from healthy volunteers. Renal disease had no effect on the half-life, but there was a 67% decline in racemic salbutamol clearance. Caution should be used when administering high doses of LEVOLIN Respules to patients with renal impairment.

Pregnancy

Pregnancy Category C

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

During marketing experience of racemic salbutamol, various congenital anomalies, including cleft palate and limb defects, have been rarely reported in the offspring of patients being treated with racemic salbutamol. Some of the mothers were taking multiple medications during their pregnancies. No consistent pattern of defects can be discerned, and a relationship between racemic salbutamol use and congenital anomalies has not been established. Because of the potential for beta-adrenergic agonists to interfere with uterine contractility, the use of levosalbutamol for the treatment of bronchospasm during labor should be restricted to those patients in whom the benefits clearly outweigh the risk.

Lactation

Plasma levels of levosalbutamol after inhalation of therapeutic doses are very low in humans, but it is not known whether levosalbutamol is excreted in human milk.

Paediatric Use

The safety and efficacy of levosalbutamol sulphate inhalation solution have been established in paediatric patients, 6 years of age and older, in an adequate and well-controlled clinical trial. Use of LEVOLIN Respules in children is also supported by evidence from adequate and well-controlled studies of levosalbutamol sulphate inhalation aerosol in adults, considering that the pathophysiology, systemic exposure of the drug, and clinical profile in paediatric and adult patients are substantially similar. Safety and effectiveness of LEVOLIN Respules in paediatric patients below the age of 6 years have not been established.

Geriatric Use

Clinical studies of levosalbutamol sulphate inhalation aerosol did not include sufficient numbers of subjects aged 65 years and older to determine whether they respond differently from 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 diseases or other drug therapy.

Salbutamol is known to be substantially excreted by the kidneys, and the risk of toxic reactions may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.
Undesirable Effects

Common side effects reported by greater than 2% in adults and adolescents were pain, back pain, allergic reaction, flu syndrome, accidental injury, tachycardia, migraine, dyspepsia, leg cramps, dizziness, hypertension, nervousness, tremor, anxiety, as well as certain respiratory effects such as increased cough, viral infection, rhinitis, sinusitis and turbinate edema. Other undesirable effects observed in less than 2% of the subjects were chills, chest pain, changes in ECG, hypertension, hypotension, syncope, diarrhoea, dry mouth, dry throat, gastroenteritis, nausea, lymphadenopathy, myalgia, hypesthesia of the hand, insomnia, paresthesia, tremor and eye itch. Common side effects observed in more than 2% of children were abdominal pain, accidental injury, asthenia, fever, headache, pain, viral infections, diarrhoea, lymphadenopathy, myalgia, asthma, pharyngitis, rhinitis, rash, urticaria; whereas in less than 2% were cyst, flu syndrome, viral infection, constipation, gastroenteritis, myalgia, hypertension, epistaxis, lung disorder, acne, herpes simplex, conjunctivitis, ear pain, dysmenorrhea, hematuria, and vaginal moniliasis. In children, frequently occurring adverse events were accidental injury, vomiting, bronchitis, pharyngitis.

The incidence of systemic beta-adrenergic adverse effects (e.g., tremor, nervousness) was low. Changes in heart rate and plasma glucose and potassium levels were slightly low.

Potentially serious hypokalaemia may result from beta₂-agonist therapy. This effect may be potentiated by hypoxia. Particular caution is advised in severe asthma in such cases, monitoring of serum potassium levels is recommended.

Post Marketing

In addition to the adverse events reported in clinical trials, the following adverse events have been observed in post approval use of levosalbutamol. These events have been chosen for inclusion due to their seriousness, their frequency of reporting, or their likely beta-mediated mechanism: angioedema, anaphylaxis, arrhythmias (including atrial fibrillation, supraventricular tachycardia, and extrasystoles), asthma, chest pain, cough increased, dysphonia dyspnea, gastrooesophageal reflux disease (GERD), metabolic acidosis, nausea, nervousness, rash, tachycardia, tremor, and urticaria. Because these events have been reported spontaneously from a population of unknown size, estimates of frequency cannot be made.

In addition, levosalbutamol, like other sympathomimetic agents, can cause adverse reactions such as hypertension, angina, vertigo, central nervous system stimulation, sleeplessness, headache, and drying or irritation of the oropharynx. If case of 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 Programme 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 with overdosage are those of excessive beta-adrenergic receptor stimulation, e.g., seizures, angina, hypertension or hypotension, tachycardia with rates upto 200 beats/min, arrhythmias, nervousness, headache, tremor, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, cardiac arrest and sleeplessness. Hypokalaemia also may occur. As with all sympathomimetic medications, cardiac arrest and even death may be associated with the abuse of levosalbutamol inhalation solution. Treatment consists of discontinuation of LEVOLIN Respules together with appropriate symptomatic therapy.

The judicious use of cardioselective beta-receptor blockers 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 LEVOLIN Respules.
Packaging Information

LEVOLIN Respules 0.31 mg ...... available as respule of 2.5 ml
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LEVOLIN Respules 1.25 mg ...... available as respule of 2.5 ml

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Last Reviewed: July 2018

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