LEVOLIN Inhaler (Levosalbutamol tartarate)

**Composition**

Each actuation delivers

- Levosalbutamol Tartrate equivalent to Levosalbutamol................. 50mcg
- Suspended in propellant HFA 134a........................................ q.s.
- Absolute Alcohol Content.....................................................7.4% v/v

**Dosage Form**

Inhalation aerosol

**Pharmacology**

**Pharmacodynamics**

Levosalbutamol is a single isomer beta₂-agonist that differs from racemic salbutamol by elimination of (S)-salbutamol.

Levosalbutamol is an effective bronchodilator whose primary mechanism of action is unimpeded by (S)-salbutamol. Therefore, when compared with racemic salbutamol, clinically comparable bronchodilation can be achieved with doses that substantially lessen beta-mediated side effects.

Activation of beta₂-adrenergic receptors on airway smooth muscle leads to the activation of adenylate cyclase and to an increase in the intracellular concentration of cyclic-3′, 5′-adenosine monophosphate (cyclic AMP). The increase in cyclic AMP is associated with the activation of protein kinase A, which in turn, inhibits the phosphorylation of myosin and lowers intracellular ionic calcium concentrations, resulting in muscle relaxation.

Levosalbutamol relaxes the smooth muscles of all airways, from the trachea to the terminal bronchioles. Increased cyclic AMP concentrations are also associated with the inhibition of the release of mediators from mast cells in the airways.

Levosalbutamol acts as a functional antagonist that relaxes the airway irrespective of the spasmogen involved, thereby protecting against all bronchoconstrictor challenges. While it is recognized that beta₂-adrenergic receptors are the predominant receptors on bronchial smooth muscle, data indicate that there are beta-receptors in the human heart, 10–50% of which are beta₂-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**

A population pharmacokinetics (PPK) model was developed using plasma concentrations of (R)-salbutamol obtained from 632 asthmatic patients, aged 4 to 81 years, in three large trials. The PPK model-derived pharmacokinetic parameters for (R)-salbutamol in paediatric and adolescent/adult patients receiving a 90 mcg dose of levosalbutamol HFA inhalation aerosol or a 180 mcg dose of racemic salbutamol by HFA metered-dose inhaler (MDI) are presented in Table 1.

These pharmacokinetics data indicate that mean exposure to (R)-salbutamol was 13–16% less in adult and 30–32% less
in paediatric patients given levosalbutamol HFA inhalation aerosol as compared to those given a comparable dose of racemic salbutamol. When compared to adult patients, paediatric patients given 90 mcg of levosalbutamol had a 17% lower mean exposure to (R)-salbutamol.

**Table1: Mean Model-Predicted (R)-Salbutamol Pharmacokinetic Parameters**

<table>
<thead>
<tr>
<th>Study Population</th>
<th>Treatment Parameters</th>
<th>Levosalbutamol</th>
<th>Racemic Salbutamol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adolescent/Adult Patients</strong></td>
<td><strong>C&lt;sub&gt;max&lt;/sub&gt; (pg/mL)</strong></td>
<td>199</td>
<td>238</td>
</tr>
<tr>
<td>(≥ 12 years)</td>
<td><strong>t&lt;sub&gt;max&lt;/sub&gt; (hr)</strong></td>
<td>0.54</td>
<td>0.53</td>
</tr>
<tr>
<td></td>
<td><strong>AUC&lt;sub&gt;(0-6)&lt;/sub&gt; (pg·hr/mL)</strong></td>
<td>695</td>
<td>798</td>
</tr>
<tr>
<td><strong>Paediatric Patients</strong></td>
<td><strong>C&lt;sub&gt;max&lt;/sub&gt; (pg/mL)</strong></td>
<td>163</td>
<td>238</td>
</tr>
<tr>
<td>(4–11 years old)</td>
<td><strong>t&lt;sub&gt;max&lt;/sub&gt; (hr)</strong></td>
<td>0.76</td>
<td>0.78</td>
</tr>
<tr>
<td></td>
<td><strong>AUC&lt;sub&gt;(0-6)&lt;/sub&gt; (pg·hr/mL)</strong></td>
<td>579</td>
<td>828</td>
</tr>
</tbody>
</table>

**Metabolism and Elimination**

Information available in published literature suggests that the primary enzyme responsible for the metabolism of salbutamol enantiomers in humans is sulphotransferase 1A3 (SULT1A3). When racemic salbutamol was administered either intravenously or via inhalation after oral charcoal administration, there was a 3- to 4-fold difference in the area under the concentration time curves (AUC) 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.

**Special Populations**

**Hepatic Impairment**

The effect of hepatic impairment on the pharmacokinetics of levosalbutamol 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 to 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 levosalbutamol to patients with renal impairment.

**Indications**

LEVOLIN Inhaler is indicated for the prevention and treatment of bronchospasm in adults, adolescents, and children 4 years of age and older with reversible obstructive airway disease.
Dosage And Administration

The recommended dosage of LEVOLIN for adults and children 4 years of age and older is 2 inhalations repeated every 4 to 6 hours; in some patients, 1 inhalation every 4 hours may be sufficient. More frequent administration or a larger number of inhalations is not routinely recommended.

If a previously effective dosage regimen fails to provide the usual response, this may be a marker of destabilization of asthma and requires re-evaluation of the patient and the treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment, e.g., corticosteroids.

Contraindications

Hypersensitivity to any of the components of the formulation. Reactions with levosalbutamol have included urticaria, angioedema, rash, bronchospasm, anaphylaxis, and oropharyngeal edema.

Warnings And Precautions

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

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 Inhaler 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 Inhaler, 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 Inhaler 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 inhalation aerosol, 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 Inhaler.

**Coexisting Conditions**

LEVOLIN Inhaler, 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.

**Hypokalemia**

As with other beta-adrenergic agonist medications, LEVOLIN Inhaler 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 bronchodilators or epinephrine should not be used concomitantly 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-adrenergic agonists such as levosalbutamol, 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 for patients with asthma. In this setting, cardioselective beta-blockers should 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. Although the clinical significance 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.

**Digoxin**

Mean decreases of 16% to 22% in serum digoxin levels were demonstrated after single-dose intravenous and oral administration of racemic salbutamol, 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 levosalbutamol 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 levosalbutamol.

**Monoamine Oxidase Inhibitors or Tricyclic Antidepressants**

LEVOLIN Inhaler 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 salbutamol on the vascular system may be potentiated. Consider alternative therapy in patients taking MAO inhibitors or tricyclic antidepressants.

### Hepatic Impairment
The effect of hepatic impairment on the pharmacokinetics of LEVOLIN Inhaler 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 Inhaler to patients with renal impairment. Racemic salbutamol is known to be substantially excreted by the kidney, and risk of toxic reactions may be greater in patients with renal impairment. 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.

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 Inhaler should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. There are clinical considerations with the use of levosalbutamol in pregnant women.

Clinical Considerations Disease-Associated Maternal and/or Embryo/Fetal Risk

In women with poorly or moderately controlled asthma, there is an increased risk of preeclampsia in the mother and prematurity, low birth weight, and small for gestational age in the neonate. Pregnant women should be closely monitored and medication adjusted as necessary to maintain optimal control.

Labor or Delivery

Levosalbutamol has not been approved for the management of preterm labor. The benefit:risk ratio when levosalbutamol is administered for tocolysis has not been established. Serious adverse reactions, including maternal pulmonary edema, have been reported during or following treatment of premature labor with beta₂-agonists, including racemic salbutamol. 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.

Lactation

Plasma concentrations of levosalbutamol after inhalation of therapeutic doses are very low in humans. It is not known whether levosalbutamol is excreted in human milk.

Pediatric Use

The safety and efficacy of levosalbutamol HFA inhalation aerosol have been established in pediatric patients, 4 years of age and older, in an adequate and well-controlled clinical trial. Use of LEVOLIN Inhaler in children is also supported by evidence from adequate and well-controlled studies of levosalbutamol HFA inhalation aerosol in adults, considering that the pathophysiology, systemic exposure of the drug, and clinical profile in pediatric and adult patients are substantially similar. Safety and effectiveness of LEVOLIN Inhaler in pediatric patients below the age of 4 years have not been established.

Geriatric Use

Clinical studies of levosalbutamol HFA 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, dizziness, asthma, pharyngitis, and rhinitis whereas those observed in children were vomiting, bronchitis and pharyngitis; 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. Potentially serious hypokalaemia may result from beta-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.

### Postmarketing Experience

In addition to the adverse events reported in clinical trials, the following adverse events have been observed in post approval use of levosalbutamol. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. 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, extrasystoles), asthma, chest pain, cough increased, dysphonia, dyspnea, gastroesophageal reflux disease (GERD), metabolic acidosis, nausea, nervousness, rash, tachycardia, tremor, and urticaria.

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 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 with overdosage are those of excessive beta-adrenergic receptor stimulation, e.g., seizures, angina, hypertension or hypotension, tachycardia with rates up to 200beats/minute, arrhythmias, nervousness, headache, tremor, dry mouth, palpitations, nausea, dizziness, fatigue, malaise, and sleeplessness. Hypokalaemia also may occur. As with all sympathomimetics, cardiac arrest and even death may be associated with the abuse of LEVOLIN Inhaler. Treatment consists of discontinuation of LEVOLIN Inhaler 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 in treating overdosage of LEVOLIN Inhaler.

### Storage And Handling Instructions
Store below 30°C
Do not freeze.

Packaging Information

LEVOLIN Inhaler with Dose Counter ............Canister containing 200 metered doses

Last Updated: November 2018
Last Reviewed: December 2018

LEVOLIN Inhaler

Source URL: https://ciplamed.com/content/levolin-inhaler