**Composition**

**LEVOLIN-1 Tablets**

Each uncoated tablet contains:

Levosalbutamol Sulphate equivalent to

Levosalbutamol ........ 1 mg

**LEVOLIN-2 Tablets**

Each uncoated tablet contains:

Levosalbutamol Sulphate equivalent to

Levosalbutamol........ 2 mg

**LEVOLIN Syrup**

Each 5 ml contains:

Levosalbutamol Sulphate equivalent to

Levosalbutamol....... 1 mg

**Dosage Form**

Oral tablet and syrup

**Pharmacology**

**Pharmacodynamics**

Activation of beta-2-adrenergic receptors on airway smooth muscle leads to the activation of adenyl 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 beta$_2$-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 beta$_1$-adrenergic receptors. The precise function of these receptors has not been established (see WARNINGS AND PRECAUTIONS). 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

Whether administered alone or as the racemate, salbutamol enantiomers are well absorbed from the gastrointestinal tract and have time to maximum drug concentration ($t_{\text{max}}$) values ranging from 45 to 360 minutes. (S)-Salbutamol has a longer $t_{\text{max}}$ when administered orally as the pure enantiomer compared with when it is administered in the racemate. This phenomenon may be due to altered gastrointestinal motility subsequent to beta-adrenoceptor stimulation by (R)-salbutamol in the racemate. The bioavailability of (S)-salbutamol is approximately 70% at both steady state and following a single oral dose, whereas the bioavailability of (R)-salbutamol increases from 9% after a single oral dose to 30% at steady state.

#### Distribution

The blood to plasma ratio for total salbutamol appears to be near unity (0.96 ± 0.13) in healthy volunteers, suggesting that the total blood clearance of salbutamol is equal to the total plasma clearance once steady state has been reached. Values for binding to blood components, along with similar volumes of distribution for salbutamol enantiomers, suggest that protein binding plays a relatively minor role in the disposition of salbutamol enantiomers.

#### Metabolism

(R)-Salbutamol was metabolized up to 12 times more efficiently than its antipode, with large, normally distributed inter-individual variation being observed in human tissue samples. It is clear from these studies that SULT1A3 expression is higher in intestine than in the other tissues studied, notably hepatic tissue. This supports clinical observations that the intestine is the main site of enantio-selective presystemic metabolism of salbutamol for drug absorbed in the gastrointestinal tract.

#### Elimination

Calculated renal clearance values for both enantiomers were significantly larger than creatinine clearance, indicating active renal excretion. This leads to relatively higher concentrations of the drug in urine than in plasma. (S)-Salbutamol is almost always found in higher amounts in urine than (R)-salbutamol, regardless of the route of administration.

### Indications

LEVOLIN Tablets and Syrup 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**

**LEVOLIN-1 and -2 Tablets/Syrup**

**Adults and Adolescents (Above 12 Years of Age)**

1–2 mg/5–10 ml three times daily.

**Children (Aged 6–11 Years)**

1 mg/5 ml three times daily.

**Contraindications**

**LEVOLIN Tablets and Syrup** are contraindicated in patients with a history of hypersensitivity to any of their components.

It should not be used for threatened abortion during the first or second trimester of pregnancy. Levosalbutamol and beta-blocking drugs such as propranolol should not usually be prescribed together.

**Warnings And Precautions**

**General**

**Paradoxical Bronchospasm**

Levosalbutamol can produce paradoxical bronchospasm, which may be life-threatening. If paradoxical bronchospasm occurs, levosalbutamol 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.

**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 levosalbutamol than usual, this may be a marker of destabilization of asthma and requires re-evaluation of the patient and treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment, e.g. corticosteroids.

**Use of Anti-Inflammatory Agents**

Levosalbutamol is not a substitute for corticosteroids. The use of 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**

Levosalbutamol like other beta-adrenergic agonists, can produce clinically significant cardiovascular
effects in some patients, as measured by heart rate, blood pressure, and symptoms. Although such effects are uncommon after administration of levosalbutamol 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, levosalbutamol, 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**

Do not exceed the 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 levosalbutamol or racemic salbutamol. Reactions have included 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 levosalbutamol.

**Coexisting Conditions**

Levosalbutamol, 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.

Changes in blood glucose may occur. Large doses of intravenous racemic salbutamol have been reported to aggravate pre-existing diabetes mellitus and ketoacidosis.

**Hypokalaemia**

As with other beta-adrenergic agonist medications, levosalbutamol may produce significant hypokalaemia 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**

**Short-Acting Bronchodilators**

Avoid concomitant use of other short-acting sympathomimetic bronchodilators or epinephrine in patients being treated 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. 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 should be considered, although they should be administered with caution.

**Diuretics**

The ECG changes or hypokalaemia that may result from the administration of non-potassium-sparing diuretics (such as loop and 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% and 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**

Levosalbutamol should be administered with extreme caution to patients being treated with monoamine oxidase (MAO) 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. Consider alternative therapy in patients taking MAO inhibitors or tricyclic antidepressants.

**Halogenated anaesthetics**

Owing to the additional antihypertensive effect, there is increased uterine inertia with risk of haemorrhage; in addition, serious ventricular rhythm disorders due to increased cardiac reactivity, have been reported on interaction with halogenated anaesthetics. Treatment should be discontinued, whenever possible, at least 6 hours before any scheduled anaesthesia with halogenated anaesthetics.

**Pregnancy**

Use of oral levosalbutamol in pregnant or nursing mothers should be considered only if the expected benefit to the mother is greater than any possible risk to the foetus or the infant.

**Lactation**

It is not known whether levosalbutamol is excreted in human milk. Caution should be exercised when oral levosalbutamol is administered to a nursing mother.
Pediatric Use

Safety and effectiveness of levosalbutamol in pediatric patients below the age of 6 years have not been established.

Geriatric Use

Clinical studies of levosalbutamol did not include sufficient numbers of subjects aged 65 years and older to determine whether they respond differently from younger subjects. If clinically warranted due to insufficient bronchodilator response, the dose of levosalbutamol may be increased in elderly patients as tolerated, in conjunction with frequent clinical and laboratory monitoring, to the maximum recommended daily dose (see Dosage and Administration).

Renal Impairment

Salbutamol is known to be substantially excreted by the kidney, 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.

Effects on ability to drive and use machines

None known.

Undesirable Effects

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. Other side effects such as palpitation, fine tremors of the skeletal muscle (particularly the hand), and muscle cramps may occur.

The other likely side effects are gastrointestinal disturbances such as nausea, vomiting, burning substernal or epigastric pain, and diarrhoea. In some cases, nervousness, headache, dizziness, fatigue, and sleeplessness may occur.

Overdosage

The expected symptoms with overdosage are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the side effects, e.g. tachycardia, nervousness, headache, tremor, nausea, dizziness, fatigue, and sleeplessness. Hypokalaemia may also occur. As with all sympathomimetic medications, cardiac arrest and even death may be associated with the abuse of levosalbutamol. Treatment consists of discontinuation of levosalbutamol 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 of levosalbutamol.

Incompatibility
Shelf-Life

LEVOLIN-1/LEVOLIN-2 Tablets: 24 months

LEVOLIN Syrup: 24 months

Storage And Handling Instructions

Store in a cool place

Protect from light

Packaging Information

LEVOLIN-1/LEVOLIN-2 Tablets: Blister pack of 10 tablets
LEVOLIN Syrup: Bottle of 100 ml

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LEVOLIN Tablets/Syrup

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