

For the use of a Registered Medical Practitioner or Hospital or a Laboratory only

CORDINE LS

1. Generic Name

Levosalbutamol, Ambroxol Hydrochloride & Guaiphenesin Syrup

2. Qualitative and quantitative Composition:

Each 5 ml contains:

Levosalbutamol Sulphate I.P.

equivalent to Levosalbutamol.....1 mg

Ambroxol Hydrochloride I.P.30 mg

Guaiphenesin I.P.50 mg

In a flavoured syrupy base.....q.s.

Colour: Tartrazine

The excipients used are Sucralose, Sodium Chloride, Sodium Benzoate, Sodium Citrate, Neotame, Raspberry Liquid Flavour, Strawberry Liquid Flavour, Tartrazine Supra Colour, Hydroxyethyl, Citric Acid Monohydrate and Menthol

3. Dosage form and strength

Dosage form: Oral Syrup (Sugar Free)

Strength: Levosalbutamol 1 mg, Ambroxol Hydrochloride 30 mg and Guaiphenesin 50 mg

4. Clinical particulars

4.1 Therapeutic indication

It is indicated for the symptomatic relief of bronchospasm in bronchial asthma & chronic bronchitis.

4.2 Posology and method of administration

Adults

5–10 mL thrice daily.

Paediatric Patients (aged 6–12 years)

5 mL thrice daily

or

As directed by the physician

4.3 Contraindications

CORDINE LS Syrup is contraindicated in patients with the following conditions:

- Known hypersensitivity to any of the components of the formulation.
- Patients with pre-existing ischaemic heart disease or those patients with significant risk factors for ischaemic heart disease.
- Patients with gastric ulceration.
- 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

4.4 Special warnings and precautions for use

Levosalbutamol Sulphate

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

Potentially serious hypokalaemia may result from beta2-agonist therapy. Particular caution is advised in acute severe asthma as this effect may be potentiated by hypoxia and by concomitant treatment with xanthine derivatives, steroids, and diuretics. Serum potassium levels should be monitored in such situations.

Cardiovascular Effects

Levosalbutamol, like all other beta-adrenergic agonists, can produce a clinically significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, and/or 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, oral levosalbutamol, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias or hypertension.

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.

Do Not Exceed The 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

Guaiifenesin

- Consult a doctor before use if your child suffers from chronic cough, if he/she has asthma or is suffering from an acute asthma attack.
- Stop use and consult a healthcare professional if your child's cough lasts for more than 5 days, comes back, or is accompanied by a fever, rash or persistent headache.
- Do not give with a cough suppressant.
- Caution should be exercised in the presence of severe renal or severe hepatic impairment.
- Not more than four doses should be given in any 24 hours. Do not exceed the stated dose.
- Do not take with any other cough and cold medicine. Consult a pharmacist or other healthcare professional before use in children under 6 years.

Ambroxol Hydrochloride

Care should be taken to avoid contact with the eyes and skin, and serious ingestion or inhalation.

In the presence of impaired renal function or severe hepatopathy, CORDINE LS Syrup may be used only after consulting a physician. In cases of severe renal failure, an accumulation of metabolites formed in the liver must be considered, and a reduction in the maintenance dose or an increase in the dose interval must be performed.

In patients with a tendency for peptic ulcers, the use of ambroxol hydrochloride should be carefully considered. In patients with malignant cilia syndrome, the advantages of secretion liquefaction should be carefully weighed against the risk of a secretory obstruction. The simultaneous administration of antitussives should definitely be avoided due to the risk of secretory obstruction (see Drug Interactions).

There have been very rare reports of severe skin lesions such as Stevens-Johnson syndrome and toxic epidermal necrolysis ([TEN], Lyell's syndrome) in temporal association with the administration of mucolytic substances such as ambroxol hydrochloride. Mostly, these could be explained by the severity of the underlying disease or concomitant medication. During the early phase of a Stevens-Johnson syndrome or TEN, a patient may first experience nonspecific influenza-like prodromes, e.g. fever, aching body, rhinitis, cough and sore throat. If new skin or mucosal lesions occur, treatment with ambroxol hydrochloride should be discontinued as a precaution. In

acute respiratory indications, medical advice should be sought if symptoms do not improve or worsen during course of therapy.

Cordine LS Syrup should be used with caution in patients with diabetes mellitus, serious cardiovascular disorders, hypertension, hyperthyroidism and peptic ulcers

4.5 Drugs interactions

Levosalbutamol Sulphate

Short-Acting Bronchodilators

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. Therefore, patients with asthma should not normally be treated with beta-blockers. 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. 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.

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 is advisable 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.

Guaiphenesin

If urine is collected within 24 hours of a dose of guaiphenesin, its metabolite may cause a colour interference with laboratory determinations of urinary 5-hydroxyindoleacetic acid (5-HIAA) and vanillylmandelic acid (VMA). Expectorants such as guaiphenesin should not be combined with cough suppressants in the treatment of cough since the combination is illogical and patients may be exposed to unnecessary adverse effects.

Ambroxol Hydrochloride

Simultaneous use of ambroxol and antibiotics (amoxicillin, cefuroxim, erythromycin, doxycyclin) results in an increase of concentration of the antibiotics in the lung tissue.

Concomitant use with antitussive agents, e.g. codeine should be avoided, because they may inhibit cough reflex.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnant Women

There are no adequate and well-controlled reported studies of this combination in pregnant women. Hence, this combination should be administered with caution in pregnancy.

Lactating Women

It is not known whether this combination is secreted in breast milk. Therefore, this combination should be used with caution in nursing mothers.

Paediatric Patients

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

Therefore, this combination should not be used for children below the age of 6 years.

Geriatric Patients

The reported 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 Posology and Method of Administration). It is not known whether this combination will have any effect on geriatric patients.

Patients with Renal Impairment

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. It is not known whether this combination will have any effect on renal impaired patients.

4.7 Effects on ability to drive and use machines

The most frequent side effects are palpitation, fine tremors of the skeletal muscle (particularly the hands) and muscle cramps (which may occur due to levosalbutamol). This may affect the ability to drive and the use of machines

4.8 Undesirable effects

Levosalbutamol Sulphate

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 hands), 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.

Guaiphenesin

The following side effects may be associated with the use of guaiphenesin:

Body System (System Organ Class)	Incidence	Adverse Drug Reactions
Immune system disorders	Not known	Hypersensitivity reactions (hypersensitivity, pruritus and urticaria) Rash
Gastrointestinal disorders	Not known	Abdominal pain upper Diarrhoea Nausea Vomiting

Ambroxol Hydrochloride

Definition of the used frequencies: common (<10% to >1%), uncommon (<1% to >0.1%), rare (<0.1%). The frequency of undesired effects, which did not appear in clinical trials but appeared only spontaneously after marketing introduction, is not known.

Immune System, Skin and Subcutaneous Tissue Disorders

Rare: rash, urticaria, hypersensitivity reactions

Frequency Not Known: anaphylactic reactions, including anaphylactic shock; angio-oedema, pruritus and other hypersensitivity reactions, severe cutaneous adverse reactions (including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis and acute generalised exanthematous pustulosis)Nervous System.

Common: dysgeusia (e.g. changed taste)

Respiratory and Gastrointestinal Disorders

Common: nausea, oral and pharyngeal hypoesthesia

Uncommon: vomiting, diarrhoea, dyspepsia, abdominal pain, dry mouth

Not Known: dry throat

Reporting of suspected adverse reactions

Torrent Pharma available at:
http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting

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

4.9 Overdose

Levosalbutamol Sulphate

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. Treatment consists of discontinuation of oral levosalbutamol together with appropriate symptomatic therapy. The judicious use of a cardio selective 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.

In the event of serious poisoning, the stomach should be emptied and, if necessary, a beta-blocker administered with caution, especially in patients with a history of bronchospasm.

Guaiphenesin

The effects of acute toxicity from guaiphenesin may include gastrointestinal discomfort, nausea and drowsiness. When taken in excess, guaiphenesin may cause renal calculi. Treatment should be symptomatic and supportive.

Ambroxol Hydrochloride

Serious intoxication symptoms have not been observed following overdose of ambroxol. Brief restlessness and diarrhoea have been reported.

Ambroxol has been tolerated well on parenteral administration up to a dosage of 15 mg/kg/day, and on oral administration up to a dosage of 25 mg/kg/day.

In analogy to preclinical examinations, increased salivation, retching, vomiting and a drop in blood pressure may occur following extreme overdose.

Based on accidental overdose and/or medication error reports, the observed symptoms are consistent with the known side effects. If symptoms of overdosage occur, symptomatic treatment should be provided.

Acute measures such as instituting vomiting and gastric lavage are not generally indicated and are only to be considered following extreme overdose. A symptomatic therapy is recommended

5 Pharmacological properties

5.1 Mechanism of Action

Levosalbutamol Sulphate

It's a β_2 adrenergic receptors on airway smooth muscle are Gs coupled and their activation by levosalbutamol leads to activation of adenylate cyclase and to an increase in the intracellular concentration of 3',5'-cyclic adenosine monophosphate (cyclic AMP). Increased cyclic AMP activates protein kinase A which itself inhibits the phosphorylation of myosin produces lower intracellular ionic calcium concentrations, inducing muscle relaxation. Increased cyclic AMP concentrations are also associated with the inhibition of the release of mediators from mast cells in the airways, potentially contributing to its benefit in asthma attacks.

Guaiphenesin

Guaifenesin is thought to act as an expectorant by increasing the volume and reducing the viscosity of secretions in the trachea and bronchi. It may aid in the flow of respiratory tract secretions, allowing ciliary movement to carry the loosened secretions upward toward the pharynx.

Ambroxol Hydrochloride

Ambroxol is a secretolytic agent used in the treatment of respiratory diseases associated with viscid or excessive mucus. The substance is a mucoactive drug with several properties including secretolytic and secretomotoric actions that restore the physiological clearance mechanisms of the respiratory tract which play an important role in the body's natural defence mechanisms. It stimulates synthesis and release of surfactant by type II pneumocytes. Surfactants acts as an anti-glue factor by reducing the adhesion of mucus to the bronchial wall, in improving its transport and in providing protection against infection and irritating agents.

5.2 Pharmacodynamic properties

Levosambutamol Sulphate

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

Levosambutamol 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. Levosambutamol acts as a functional antagonist that relaxes the airway irrespective of the spasmogen involved, thereby protecting against all bronchoconstrictor challenges. While it is recognised 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.

Guaiphenesin

Guaiphenesin is thought to exert its pharmacological action by stimulating receptors in the gastric mucosa. This increases the output from secretory glands of the gastrointestinal system and reflexly increases the flow of fluids from glands lining the respiratory tract. The result is an increase in volume and decrease in the viscosity of bronchial secretions. Other actions may include stimulating vagal nerve endings in bronchial secretory glands and stimulating certain centres in the brain, which, in turn, enhance respiratory fluid flow. Guaiphenesin produces its expectorant action within 24 hours.

Ambroxol Hydrochloride

Ambroxol, a substituted benzylamine, is a metabolite of bromhexine. It differs from bromhexine by the absence of a methyl group and the introduction of a hydroxyl group in the para-trans position of the cyclohexyl ring.

Ambroxol hydrochloride causes an increase of the secretion in the respiratory tract. It enhances pulmonary surfactant production and stimulates ciliary activity. These actions result in improved mucus flow and transport (mucociliary clearance). Improvement of mucociliary clearance has been shown in clinical pharmacologic studies. Enhancement of fluid secretion and mucociliary clearance facilitates expectoration and reduces cough. Cytokine release from blood and also mononuclear and polymorphonuclear cells was found to be significantly reduced by ambroxol hydrochloride in vitro. The reported clinical relevance of these findings is still unknown.

5.3 Pharmacokinetic properties

Levosalmamol Sulphate

Absorption

Whether administered alone or as the racemate, salbutamol enantiomers are well absorbed from the gastrointestinal tract and time to maximum drug concentration (t_{max}) values ranges from 45 to 360 minutes. (S)-Salbutamol has a longer t_{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 metabolised 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 intestines are the main site of enantio-selective pre-systemic 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.

Guaiphenesin

Absorption

Guaiphenesin is well absorbed from the gastrointestinal tract following oral administration, although limited information regarding its pharmacokinetics is available. After the administration of 600 mg guaiphenesin to healthy adult volunteers, the C_{max} was approximately 1.4 ug/mL, with T_{max} occurring approximately 15 minutes after drug administration.

Distribution

No information is available on the distribution of guaiphenesin in humans.

Metabolism and Elimination

Guaiphenesin appears to undergo both oxidation and demethylation. Following an oral dose of 600 mg guaiphenesin to 3 healthy male volunteers, the $t_{1/2}$ was approximately 1 hour and the drug was not detectable in the blood after approximately 8 hours.

Pharmacokinetics in Patients with Renal/Hepatic Impairment

There have been no specific studies of guaiphenesin in subjects with renal or hepatic impairment. Caution is, therefore, recommended when administering this product to subjects with severe renal or hepatic impairment.

Pharmacokinetics in Geriatric Patients

Not applicable.

Ambroxol Hydrochloride

Absorption

Ambroxol is rapidly absorbed (70–80%) after oral administration. The time to reach peak plasma concentration is approximately 2 hours.

Distribution

Distribution after oral, intramuscular and intravenous administration from blood to organs is rapid, with maximal concentrations in the lungs. Plasma half-life is 7–12 hours, and accumulation has not been observed

Metabolism

Primary metabolism of ambroxol takes place in the liver by conjugation. The metabolite is dibromoanthranilic acid (activity unspecified).

Excretion

Excretion is primarily via the kidneys. Renal clearance (rate) is approximately 53 mL/minute; approximately 5–6% of a dose is excreted unchanged in the urine. The elimination half-life of ambroxol is biphasic, with an alpha half-life of 1.3 hours and a beta half-life of 8.8 hours.

6. Nonclinical properties

Preclinical data based on reported conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential show no particular risk for humans.

Acute Toxicity

Ambroxol hydrochloride has a low index for acute toxicity.

Chronic Toxicity/Subchronic Toxicity

Investigations of chronic toxicity in two animal species have shown no substance-induced changes.

In recorded repeat-dose studies, oral doses of 150 mg/kg/day (mouse, 4 weeks), 50 mg/kg/day (rat, 52 and 78 weeks), 40 mg/kg/day (rabbit, 26 weeks) and 10 mg/kg/day (dog, 52 weeks) were the no-observed adverse effect level (NOAEL). No toxicological target organs were detected. Further, 4-week intravenous toxicity studies with ambroxol hydrochloride in rats (4, 16 and 64 mg/kg/day) and in dogs (45, 90 and 120 mg/kg/day (infusion over 3 hours/day)) showed no severe local and systemic toxicity including histopathology. All adverse effects were reversible.

Mutagenic and Tumourigenic Potential

Genotoxicity reported studies in vitro (Ames and chromosome aberration test) and in vivo (mouse micronucleus test) did not reveal any mutagenic potential of ambroxol hydrochloride. Ambroxol hydrochloride did not show any tumourigenic potential in carcinogenicity studies in mice (50, 200 and 800 mg/kg/day) and rats (65, 250 and 1,000 mg/kg/day) when treated with a dietary admixture for 105 and 116 weeks, respectively.

Reproductive Toxicity

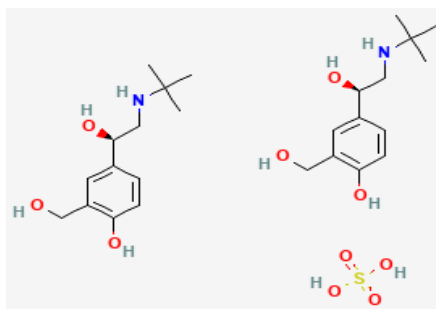
In reported studies Ambroxol hydrochloride was neither embryotoxic nor teratogenic when tested at oral doses up to 3,000 mg/kg/day in rats and up to 200 mg/kg/day in rabbits. The fertility of male and female rats was not affected up to 500 mg/kg/day. The NOAEL in the peri- and post-natal development study was 50 mg/kg/day.

At 500 mg/kg/day, ambroxol hydrochloride was slightly toxic for dams and pups, as shown by a retarded body-weight development and reduced litter size. Ambroxol crosses the placental barrier and passes into breast milk in animals.

7. Description

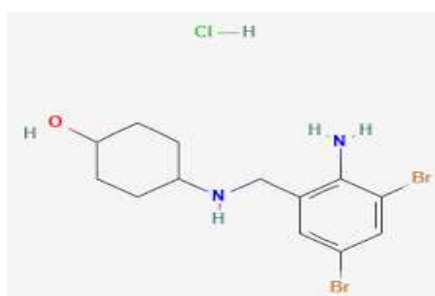
Levosambutamol Sulphate

Levosambutamol Sulphate is 4-[(1R)-2-(tert-butylamino)-1-hydroxyethyl]-2-(hydroxymethyl)phenol;sulfuric acid with molecular weight of 576.7 and empirical formula is $C_{26}H_{44}N_2O_{10}S$. The chemical structure is:



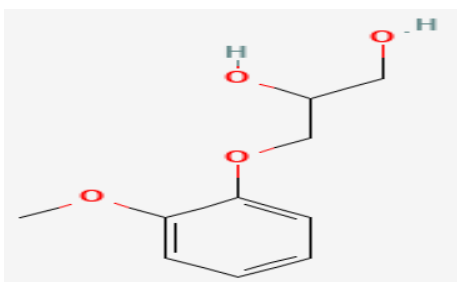
Ambroxol Hydrochloride

Ambroxol Hydrochloride is trans-4-[(2-amino-3,5-dibromobenzyl)amino]cyclohexanol hydrochloride with molecular weight of 414.56 and empirical formula is $C_{13}H_{18}Br_2N_2O$, HCl. The chemical structure is:



Guaiphenesin

Guaiphenesin is 3-(2-methoxyphenoxy)propane-1,2-diol with molecular weight of 198.22 and empirical formula is $C_{10}H_{14}O_4$. The chemical structure is:



Levosalbutamol, Ambroxol Hydrochloride & Guaiphenesin Syrup is yellow coloured solution filled in amber colour PET bottle having flavoured odour. The excipients used are Sucralose, Sodium Chloride, Sodium Benzoate, Sodium Citrate, Neotame, Raspberry Liquid Flavour, Strawberry Liquid Flavour, Tartrazine Supra Colour, Hydroxyethyl, Citric Acid Monohydrate and Menthol.

8 Pharmaceutical particulars

8.1 Incompatibilities

Not Applicable

8.2 Shelf-life

Do not use later than date of expiry.

8.3 Packaging information

CORDINE LS is available in 100ml amber PET bottle.

8.4 Storage and handing instructions

- Store below 30°C. Protect from light.
- Keep out of reach of children.
- Shake well before use.

9 Patient Counselling Information

Package leaflet: Information for the user

CORDINE LS

Levosalbutamol, Ambroxol Hydrochloride & Guaiphenesin Syrup

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

- 9.1. What CORDINE LS and what they are used for
- 9.2. What you need to know before you take CORDINE LS
- 9.4. Possible side effects
- 9.5. How to store CORDINE LS Tablets
- 9.6. Contents of the pack and other information

9.1 What is CORDINE LS and what it is used for

CORDINE LS Syrup is a combination of three medicines: Ambroxol, Levosalbutamol and Guaifenesin, which relieves cough with mucus. Ambroxol is a mucolytic which thins and loosens mucus (phlegm), making it easier to cough out. Levosalbutamol is a bronchodilator. It works by relaxing the muscles in the airways and widens airways. Guaifenesin is an expectorant which decreases the stickiness of mucus (phlegm) and helps in its removal from the airways. Together, they make breathing easier

CORDINE LS Syrup is indicated for the symptomatic relief of bronchospasm in bronchial asthma & chronic bronchitis.

9.2 What you need to know before you take CORDINE LS

Do not take CORDINE LS if you have following conditions:

- Known hypersensitivity to any of the components of the formulation.
- Patients with pre-existing ischaemic heart disease or those patients with significant risk factors for ischaemic heart disease.
- Patients with gastric ulceration.
- 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

Talk to your doctor or pharmacist before taking Cordine LS.

Levosalbutamol Sulphate

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 recognised that paradoxical bronchospasm, when associated with inhaled formulations, frequently occurs with the first use.

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Asthma may deteriorate acutely over a period of hours, or chronically over several days or longer. If the patient needs more doses of oral levosalbutamol than usual, this may be a marker of destabilisation of asthma and requires re-evaluation of the patient and the treatment regimen, with special consideration to the possible need for anti-inflammatory treatment, e.g. corticosteroids.

Potentially serious hypokalaemia may result from beta2-agonist therapy. Particular caution is advised in acute severe asthma as this effect may be potentiated by hypoxia and by concomitant treatment with xanthine derivatives, steroids, and diuretics. Serum potassium levels should be monitored in such situations.

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should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias or hypertension.

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.

Do Not Exceed The 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

Guaiifenesin

- Consult a doctor before use if your child suffers from chronic cough, if he/she has asthma or is suffering from an acute asthma attack.
- Stop use and consult a healthcare professional if your child's cough lasts for more than 5 days, comes back, or is accompanied by a fever, rash or persistent headache.
- Do not give with a cough suppressant.
- Caution should be exercised in the presence of severe renal or severe hepatic impairment.
- Not more than four doses should be given in any 24 hours. Do not exceed the stated dose.
- Do not take with any other cough and cold medicine. Consult a pharmacist or other healthcare professional before use in children under 6 years.

Ambroxol Hydrochloride

Care should be taken to avoid contact with the eyes and skin, and serious ingestion or inhalation.

In the presence of impaired renal function or severe hepatopathy, CORDINE LS Syrup may be used only after consulting a physician. In cases of severe renal failure, an accumulation of metabolites formed in the liver must be considered, and a reduction in the maintenance dose or an increase in the dose interval must be performed.

In patients with a tendency for peptic ulcers, the use of ambroxol hydrochloride should be carefully considered. In patients with malignant cilia syndrome, the advantages of secretion liquefaction should be carefully weighed against the risk of a secretory obstruction. The simultaneous administration of antitussives should definitely be avoided due to the risk of secretory obstruction.

There have been very rare reports of severe skin lesions such as Stevens-Johnson syndrome and toxic epidermal necrolysis ([TEN], Lyell's syndrome) in temporal association with the administration of mucolytic substances such as ambroxol hydrochloride. Mostly, these could be explained by the severity of the underlying disease or concomitant medication. During the early phase of a Stevens-Johnson syndrome or TEN, a patient may first experience nonspecific influenza-like prodromes, e.g. fever, aching body, rhinitis, cough and sore throat. If new skin or mucosal lesions occur, treatment with ambroxol hydrochloride should be discontinued as a precaution. In acute respiratory indications, medical advice should be sought if symptoms do not improve or worsen during course of therapy.

Cordine LS Syrup should be used with caution in patients with diabetes mellitus, serious cardiovascular disorders, hypertension, hyperthyroidism and peptic ulcers

If any of the above applies to you, talk straight away to your doctor before or while taking Cordine LS syrup.

Talk to your doctor if any of the above applies to you. Cordine LS may not be suitable for you. Your doctor will advise you.

Pregnant Women

There are no adequate and well-controlled studies recorded of this combination in pregnant women. Hence, this combination should be administered with caution in pregnancy.

Lactating Women

It is not known whether this combination is secreted in breast milk. Therefore, this combination should be used with caution in nursing mothers.

Paediatric Patients

Safety and effectiveness of levosalbutamol in paediatric patients below the age of 6 years have not been established. Therefore, this combination should not be used for children below the age of 6 years.

Geriatric Patients

According to recorded 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. It is not known whether this combination will have any effect on geriatric patients.

Patients with Renal Impairment

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.

It is not known whether this combination will have any effect on renal impaired patients.

Other medicines and CORDINE LS

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Make sure to tell your doctor if you are taking any of the following medicines, as a dose adjustment of Cordine OD or monitoring should be required:

Levosalbutamol Sulphate

Short-Acting Bronchodilators

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. Therefore, patients with asthma should not normally be treated with beta-blockers. 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. 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.

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 is advisable 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.

Guaiphenesin

If urine is collected within 24 hours of a dose of guaiphenesin, its metabolite may cause a colour interference with laboratory determinations of urinary 5-hydroxyindoleacetic acid (5-HIAA) and vanillylmandelic acid (VMA).

Expectorants such as guaiphenesin should not be combined with cough suppressants in the treatment of cough since the combination is illogical and patients may be exposed to unnecessary adverse effects.

Ambroxol Hydrochloride

Simultaneous use of ambroxol and antibiotics (amoxicillin, cefuroxim, erythromycin, doxycyclin) results in an increase of concentration of the antibiotics in the lung tissue.

Concomitant use with antitussive agents, e.g. codeine should be avoided, because they may inhibit cough reflex.

Driving and using machines

The most frequent side effects are palpitation, fine tremors of the skeletal muscle (particularly the hands) and muscle cramps (which may occur due to levosalbutamol). This may affect the ability to drive and the use of machines.

9.3 How to take CORDINE LS

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

If you take more CORDINE LS than you should:

Levosalbutamol Sulphate

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. Treatment consists of discontinuation of oral levosalbutamol together with appropriate symptomatic therapy. The judicious use of a cardio selective 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.

In the event of serious poisoning, the stomach should be emptied and, if necessary, a beta-blocker administered with caution, especially in patients with a history of bronchospasm.

Guaiphenesin

The effects of acute toxicity from guaiphenesin may include gastrointestinal discomfort, nausea and drowsiness. When taken in excess, guaiphenesin may cause renal calculi. Treatment should be symptomatic and supportive.

Ambroxol Hydrochloride

Serious intoxication symptoms have not been observed following overdose of ambroxol. Brief restlessness and diarrhoea have been reported.

Ambroxol has been tolerated well on parenteral administration up to a dosage of 15 mg/kg/day, and on oral administration up to a dosage of 25 mg/kg/day.

In reported analogy to preclinical examinations, increased salivation, retching, vomiting and a drop in blood pressure may occur following extreme overdose.

Based on accidental overdose and/or medication error reports, the observed symptoms are consistent with the known side effects. If symptoms of overdosage occur, symptomatic treatment should be provided.

Acute measures such as instituting vomiting and gastric lavage are not generally indicated and are only to be considered following extreme overdose. A symptomatic therapy is recommended.

If you forget to take CORDINE LS

If you forget to take a dose of Cordine- LS, take the next dose at the usual time. Do not take a double dose to make up for the forgotten dose.

If you stop taking CORDINE LS

As the treatment for bronchospasm in bronchial asthma & chronic bronchitis is usually life-long, you should discuss with your doctor before stopping this medicinal product.

If you think that the effect of CORDINE LS is too strong or too weak, talk to your doctor or pharmacist.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

9.4 Possible side effects

Levosulbutamol Sulphate

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 hands), 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.

Guaiphenesin

The following side effects may be associated with the use of guaiphenesin:

Body System (System Organ Class)	Incidence	Adverse Drug Reactions
Immune system disorders	Not known	Hypersensitivity reactions (hypersensitivity, pruritus and urticaria) Rash
Gastrointestinal disorders	Not known	Abdominal pain upper Diarrhoea

		Nausea Vomiting
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Ambroxol Hydrochloride

Definition of the used frequencies: common (<10% to >1%), uncommon (<1% to >0.1%), rare (<0.1%). The frequency of undesired effects, which did not appear in clinical trials but appeared only spontaneously after marketing introduction, is not known.

Immune System, Skin and Subcutaneous Tissue Disorders

Rare: rash, urticaria, hypersensitivity reactions

Frequency Not Known: anaphylactic reactions, including anaphylactic shock; angio-oedema, pruritus and other hypersensitivity reactions, severe cutaneous adverse reactions (including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis and acute generalised exanthematous pustulosis)

Nervous System.

Common: dysgeusia (e.g. changed taste)

Respiratory and Gastrointestinal Disorders

Common: nausea, oral and pharyngeal hypoesthesia

Uncommon: vomiting, diarrhoea, dyspepsia, abdominal pain, dry mouth

Not Known: dry throat

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of Torrent Pharma available at:

http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting

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

9.5 How to store CORDINE LS

- Store below 30°C. Protect from light
- Keep out of reach of children.
- Shake well before use.

9.6 Contents of the pack and other information

The active substances are Levosalbutamol ,Ambroxol Hydrochloride.

The Other ingredients are Sucralose, Sodium Chloride, Sodium Benzoate, Sodium Citrate, Neotame, Raspberry Liquid Flavour, Strawberry Liquid Flavour, Tartrazine Supra Colour, Hydroxyethyl, Citric Acid Monohydrate and Menthol

CORDINE LS is available in 100ml amber PET bottle.

10 Details of manufacturer

Manufactured in India by:

Ravenbhel Biotech

EPIP, SIDCO, Kartholi- Bari Brahmana, Jammu

11 Details of permission or licence number with date

Mfg Lic No JK/01/11-12/192

12. Date of revision

Not Applicable

MARKETED BY



TORRENT PHARMACEUTICALS LTD.

IN/ CORDINE LS 1 mg/50 mg/Oct-21/01/PI