For the use only of Registered Medical Practitioner

1. Generic Name and Brand Name

Levosalbutamol Sulphate, Ambroxol Hydrochloride & Guaiphenesin Syrup
DELETUS® LS JR

2. Qualitative and Quantitative Composition:

Each 5 ml contains:
Levosalbutamol Sulphate I.P.
Eq. to Levosalbutamol……....0.5 mg
Ambroxol Hydrochloride I.P...15 mg
Guaiphenesin I.P……..50 mg
Flavoured Syrup Base……..q.s.
Colour: Ponceau 4R

3. Dosage Form & strength

Refer section 1 & 2

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

It should be given in a dose and duration as directed by the physician.

Posology
Adults and Adolescents (Above 12 Years of Age):
The usual recommended oral dose is 5 – 10 ml, 2 to 3 times daily or as directed by the Physician.
Children (6-12 years):
Start with 2.5 ml thrice daily and increase to 5 ml of syrup 2-3 times daily or as directed by the Physician.
For children less than 6 years of age, consult a physician or child specialist; the dose should be individualized.
Method of administration: For oral administration only.
Do not exceed the recommended dosage, unless advised by the Physician. Shake the bottle before use.

4.3 Contraindications

It is contraindicated in patients with known hypersensitivity to any of the components of the formulation.
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.
It must not be used in children under two years.

4.4 Special warnings and precautions for use

Levosalbutamol

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.

Hypokalemia
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.

Ambroxol
There have been reports of severe skin reactions such as erythema multiforme, Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) and acute generalised exanthematous pustulosis (AGEP) associated with the administration of ambroxol. Mostly these could be explained by the severity of the patient's underlying disease and/or concomitant medication. In addition during the early phase of a Stevens - Johnson syndrome or TEN a patient may first experience non-specific influenza-like prodromes like e.g. fever, aching body, rhinitis, cough and sore throat. Misled by these non-specific influenza-like prodromes it is possible that a symptomatic treatment is started with a cough and cold medication. Therefore if new skin or mucosal lesions occur, medical advice should be sought immediately and treatment with ambroxol hydrochloride discontinued as a precaution.

If symptoms or signs of a progressive skin rash (sometimes associated with blisters or mucosal lesions) are present, ambroxol treatment should be discontinued immediately and medical advice should be sought. Because of a possible build-up of secretion, Ambroxol should only be used with caution in disturbed bronchomotor function and large quantities of secretion (e.g. in the rare primary ciliary dyskinesia).

In the presence of impaired renal function or severe hepatopathy, ambroxol may be used only after consulting a physician. As for any medication with hepatic metabolism followed by renal elimination, accumulation of the metabolites of ambroxol generated in the liver can be expected in the presence of severe renal insufficiency. It must only be used with particular caution (i.e. at longer intervals or at a reduced dose) in impaired renal function or a severe hepatic disease. In severe renal insufficiency, an accumulation of the metabolites of ambroxol formed in the liver must be expected.

Caution should be exercised in patients with histamine intolerance. Long-term therapy should be avoided in these patients, as ambroxol influences the histamine metabolism and may lead to symptoms of intolerance (e.g. headache, runny nose, itching).

Care to be taken to avoid contact with eye, skin, serious ingestion or inhalation.
Since mucolytics may disrupt the gastric mucosal barrier ambroxol should be used with care in patients with a history of peptic ulcer disease.

Paediatric population
Persistent or recurrent cough in children between 2-4 years requires medical diagnosis before treatment.

Guaiphenesin
Guaiphenesin should be not used for persistent or chronic cough, such as occurs with asthma, or where cough is accompanied by excessive secretions, unless directed by a physician. A persistent cough may be a sign of a serious condition. If cough persists for more than 7 days, tends to recur, or is accompanied by a fever, rash, or persistent headache, a physician should be consulted. Caution should be exercised in the presence of severe renal or severe hepatic impairment. The concomitant use of cough suppressants is not recommended. Patients with rare hereditary problems of fructose intolerance should not take this medicine. Not more than 4 doses should be given in any 24 hours. Avoid with any other cough and cold medicine. Consult a pharmacist or other healthcare professional before use in children under 6 years. Stop use and ask a healthcare professional if your cough lasts for more than 5 days, comes back, or is accompanied by a fever, rash, or persistent headache. Do not take with a cough suppressant. Do not give this medicine with any other cough or cold medicines.

Others
This product or expectorant containing formulation should be used with caution in patients with diabetes mellitus, serious cardiovascular disorders, hypertension, hyperthyroidism and peptic ulcers.
Do not give this medicine with any other cough or cold medicines.

4.5 Drug Interactions
Levosalbutamol
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.

Ambroxol
No clinically relevant unfavorable interaction with other medications has been reported. Simultaneous use of ambroxol and antibiotics (amoxicillin, cefuroxime, erythromycin, and doxycycline) 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. On combined use of ambroxol with antitussives (cough-suppressant medicines), a dangerous build-up of secretion may develop due to the impaired cough reflex, meaning that the indication for this combination treatment should be examined particularly carefully.

Guaiphenesin
Diagnostic Interference
Guaiphenesin has been shown to produce a colour interference with certain clinical laboratory determinations of 5-hydroxyindoleacetic acid (5-HIAA) and vanilmandelic acid (VMA). Guaiphenesin could interfere with the diagnosis of carcinoid syndrome. Patients being evaluated for carcinoid syndrome should therefore discontinue any preparation containing guaiphenesin for

24 hours before collection of urine specimens for the determination of 5-hydroxy indole acetic acid(5-HIAA).

4.6 Use in special populations (Pregnancy, Nursing woman, Pediatric use, Geriatric use)

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.

There are no sufficient data for the use of ambroxol in pregnant women. Ambroxol hydrochloride crosses the placental barrier. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Extensive clinical experience after the 28th week of pregnancy has shown no evidence of harmful effects on the foetus. Nonetheless, the usual precautions regarding the use of drugs during pregnancy should be observed. Especially during the first trimester, the use of ambroxol is not recommended.

Available evidence and/or expert consensus for guaiphenesin are inconclusive or are inadequate for determining infant risk when used during pregnancy and breastfeeding. Weigh the potential benefits of drug treatment against potential risks before taking this drug during pregnancy and breastfeeding. Although adequate and well-controlled studies in pregnant women have not been performed, the Collaborative Perinatal Project monitored 197 mother-child pairs exposed to guaifenesin during the first trimester. An increased occurrence of inguinal hernias was found in the neonates. However, congenital defects were not strongly associated with guaifenesin use during pregnancy in 2 large groups of mother-child pairs.

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.
Ambroxol hydrochloride is excreted in breast milk. Although unfavorable effects on breastfed infants would not be expected, ambroxol is not recommended for use in nursing mothers. As there is no adequate experience in humans to date, ambroxol should only be used in lactation after careful benefit/risk assessment.

Guaiphenesin is excreted in breast milk in small quantities. Caution should therefore be exercised by balancing the potential benefit of treatment against any possible risks.

Pediatric population

For children under 2 years of age, use of this syrup is not recommended, however it is advised to consult with the Physician.

Elderly population

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.

In elderly patients or in those known to be unusually sensitive to beta-adrenergic stimulant drugs, it is advisable to initiate treatment with lowest possible doses.
In addition, the dose selection for an elderly patient should be cautious, usually starting at the lower end of the dose range, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other drug therapy.

In patients with liver impairment
Use with caution.

In patients with 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. Use with caution.

4.7 Effects on ability to drive and use machines
Studies on the effects on the ability to drive and use machines have not been performed. However, it is advised to take precautions if driving or operating a machine.

4.8 Undesirable effects
Levosalbutamol
Potentially serious hypokalemia 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.

The most common side effect of Salbutamol 2mg/5ml oral solution is fine tremor of the hands, which may interfere with precise manual work. Tension, restlessness and a rapid heartbeat may also occur. There have been very rare reports of muscle cramps. Hypersensitivity reactions such as angioedema, urticaria, bronchospasm, hypotension and collapse have rarely been reported. Potentially serious hypokalaemia may result from β2-agonist therapy. Occasional headaches have also been reported. As with other drugs in this class rare reports of hyperactivity in children have been reported.

Ambroxol
Under individual hypersensitivity to Ambroxol allergic reactions such as skin rash, nettle-rash, and angioneurotic oedema are possible. Under the prolonged administration in large doses pain in epigastrial area, nausea, vomiting can appear.

Frequency categories for adverse reactions are defined using the following convention: Very common: (≥1/10), Common: (≥1/100 to <1/10), Uncommon: (≥1/1,000 to <1/100), Rare: (≥1/10,000 to <1/1,000) Very rare: (<1/10,000), Not known: (cannot be estimated from the available data).
Gastrointestinal Disorders: Common: Nausea. Uncommon: Vomiting, diarrhoea, dry mouth, dyspepsia, and abdominal pain.
Respiratory, Mediastinal and Thoracic Disorders: Common: Oral and pharyngeal hypaesthesia. Not known: Dry throat.
Nervous System Disorders: Common: Dysgeusia (e.g. changed taste).
Immune System Disorders: Uncommon: Fever. Rare: Hypersensitivity reactions. Not known: Anaphylactic reactions including anaphylactic shock, angioedema and pruritus.
Skin and Sub cutaneous Tissue Disorders: Rare: Rash, urticaria. Not known: Severe cutaneous adverse reactions (including erythema multiforme, Stevens-Johnson syndrome/toxic epidermal necrolysis and acute generalized exanthematous pustulosis).

Guaiphenesin
Gastrointestinal discomfort, nausea, and vomiting have occasionally been reported with guaifenesin, particularly in very large doses. Others include dizziness, diarrhoea, headache and rash (including urticaria). Also, hypersensitivity reactions may occur.
The frequency of these guaifenesin-related adverse reactions is unknown but based on estimate from post-marketing data are likely to be rare: Allergic reactions, angioedema, anaphylactic reactions, dyspnoea (reported in association with other symptoms of hypersensitivity), nausea, vomiting, abdominal discomfort, rash, and urticaria.

Reporting of side effects or suspected adverse reaction: If you experience any side effects, talk to your doctor or pharmacist or report to indiadrugsafety@akums.in. 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.

4.9 Overdose
Levosalbutamol
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 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.

Ambroxol
No specific overdose symptoms have been reported in man to date. Based on accidental overdose and/or medication error reports the observed symptoms are consistent with the known side effects of ambroxol hydrochloride at recommended doses and may need symptomatic treatment.

Acute potential health effects include skin irritation, eye irritation, respiratory tract irritation, gastrointestinal tract irritation with decreased motility or constipation, ulceration or bleeding from the stomach or duodenum, peritonitis. It may even affect behavior/central nervous system (tremor, convulsions, ataxia, and somnolence), respiration (dyspnea, respiratory stimulation), liver, blood (changes if white blood cell count), and urinary system. No data available on chronic potential health effects.

Guaiphenesin
The effects of acute toxicity from guaifenesin may include gastrointestinal discomfort, nausea and drowsiness. The drug is, however, rapidly metabolized and excreted in the urine. Patients should be kept under observation and treated symptomatically. Overdosage may also give rise to nausea and vomiting. Treatment need only be symptomatic and supportive.

In the event of overdosage, discontinue medication and seek medical help immediately

5. Pharmacological properties

5.1 Mechanism of action

Levosalbutamol actives the beta2-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.

Ambroxol is a mucolytic agent. Excessive Nitric oxide (NO) is associated with inflammatory and some other disturbances of airways function. NO enhances the activation of soluble guanylate cyclase and cGMP accumulation. Ambroxol has been shown to inhibit the NO-dependent activation of soluble guanylate cyclase. It is also possible that the inhibition of NO-dependent activation of soluble guanylate cyclase can suppress the excessive mucus secretion, therefore it lowers the phlegm viscosity and improves the mucociliary transport of bronchial secretions.

Guaifenesin is a mucoactive drug expectorant which increases the amount of output of bronchial secretions and sputum by reducing the viscosity of the secretions. It reduces the surface tension and adhesiveness of sputum.By reducing the adhesiveness and viscosity of sputum, It increases the efficacy of cough reflex, ciliary actions and mucociliary removal for accumulated bronchial secretions from the lower and upper airway

5.2 Pharmacodynamic Properties

Levosalbutamol

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.

Ambroxol
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 clinical relevance of these findings is still unknown. Ambroxol is more effective, than its predecessor - Bromhexine; it is non-toxic one and well endured by patients.

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 viscosity of bronchial secretions. Other actions may include stimulating vagal nerve endings in bronchial secretory glands and stimulating certain centers in the brain, which in turn enhance respiratory fluid flow. Guaiphenesin produces its expectorant action within 24 hours.

5.3 Pharmacokinetic properties
Levosalbutamol
Absorption: Whether administered alone or as the racemate, salbutamol enantiomers are well absorbed from the gastrointestinal tract and have time to maximum drug concentration (tmax) values ranging from 45 to 360 minutes. (S)-Salbutamol has a longer tmax 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.

Ambroxol
Absorption: Absorption of all immediate release oral forms of Ambroxol hydrochloride is rapid and complete, with dose linearity in the therapeutic range. Maximum plasma levels are reached within 1 to 2.5 hours following oral administration of the immediate-release formulation and after a median of 6.5 hours for the slow release formulation. The absolute bioavailability after a 30 mg tablet was found to be 79%.The slow release capsule showed a relative availability of 95% (dose-normalized) in comparison to a daily dose of 60 mg (30 mg twice daily) administered as immediate release tablet.

Distribution
Distribution of Ambroxol hydrochloride from blood to tissue is rapid and pronounced, with the highest concentration of the active substance found in the lungs. The volume of distribution following oral administration was estimated to be 552 L. In the therapeutic range, plasma protein binding was found to be approximately 90%.

Metabolism and elimination
About 30% of an orally administered dose is eliminated via first pass metabolism. Ambroxol hydrochloride is primarily metabolized in the liver by glucuronidation and some cleavage to dibromanthranilic acid (approximately 10% of dose) aside from some minor metabolites. Studies in human liver microsomes have shown that CYP3A4 is responsible for the metabolism of ambroxol hydrochloride to dibromanthranilic acid.

Within 3 days of oral administration, approximately 6% of the dose is found in free form, while approximately 26 % of the dose is recovered in a conjugated form in the urine.
Ambroxol hydrochloride is eliminated with a terminal elimination half-life of approximately 10 hours. Total clearance is in the range of 660 mL/min, with renal clearance accounting for approximately 8% of the total clearance. It has been estimated that the amount of dose excreted in urine after 5 days represents about 83% of total dose (radioactivity).

Pharmacokinetics in special populations: In patients with hepatic dysfunction elimination of ambroxol hydrochloride is reduced, resulting in approximately 1.3 to 2-fold higher plasma levels. Due to the high therapeutic range of ambroxol hydrochloride, dose adjustments are not necessary.

Guaiphenesin
Absorption: Guaiphenesin is well absorbed from the gastro-intestinal 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 1.4ug/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 guaifenesin to 3 healthy male volunteers, the t½ was approximately 1 hour and the drug was not detectable in the blood after approximately 8 hours.
Pharmacokinetics in 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.

6. Nonclinical properties

Animal Toxicology/Pharmacology
In common with other potent selective β2-agonists, salbutamol has been shown to be teratogenic in mice when given subcutaneously. In a reproductive study, 9.3% of fetuses were found to have cleft palate at 2.5mg/kg dose, 4 times the maximum human oral dose. In rats, treatment at the levels of 0.5, 2.32, 10.75 and 50mg/kg/day orally throughout pregnancy resulted in no significant foetal abnormalities. The only toxic effect was an increase in neonatal mortality at the highest dose level as the result of lack of maternal care. Reproductive studies in the rabbit at doses of 50mg/kg/day orally (i.e. much higher than the normal human dose) have shown foetuses with treatment related changes; these included open eyelids (ablepharia), secondary palate clefts (palatoschisis), changes in ossification of the frontal bones of the cranium (cranioschisis) and limb flexure.

In an oral fertility and general reproductive performance study in rats at doses of 2 and 50 mg/kg/day, with the exception of a reduction in number of weanlings surviving to day 21 post-partum at 50 mg/kg/day, there were no adverse effects on fertility, embryofoetal development, litter size, birth weight or growth rate.

Ambroxol Hydrochloride
Preclinical data based on 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/sub chronic Toxicity
Investigations of chronic toxicity in two animal species have shown no substance-induced changes.

In 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 Tumorigenic Potential
Genotoxicity 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 tumorigenic 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.

7. Description
Deletus LS JR is supplied for oral administration.
Each 5 ml of Deletus LS JR contains Levosalbutamol Sulphate eq. to Levosalbutamol 0.5 mg, Ambroxol Hydrochloride 15 mg & Guaiphenesin 50 mg.

8. Pharmaceutical particulars
8.1 Incompatibilities
Not known

8.2 Shelf Life
Refer Pack

8.3 Packaging Information
Refer Pack

8.4 Storage condition & handling instructions
Refer Pack

9. Patient Counseling Information
Do not give this medicine to children below 2 years of age.
Do not exceed the recommended dose. If symptoms persist, consult your doctor.
Please discuss with your doctor if you are taking any medication which is contraindicated
Do not take this medicine if you are allergic to any of its ingredients.
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines such as the following:

- Antibiotics (amoxicillin, cefuroxime, and erythromycin) – these lead to increase of antibiotic concentrations in the mucus formed in the airways, which may be considered as a desirable effect.

- The concomitant use of medicines that inhibit cough (e.g. codeine) is not recommended since these medicines suppress the mucus expectoration.
- Other short-acting sympathomimetic bronchodilators or epinephrine, diuretics, digoxin, beta-blockers, monoamine oxidase inhibitors or tricyclic antidepressants, halogenated anesthetics.

10. Details of manufacturer
Refer Pack for manufacturer details.

Marketed by:
Abbott Healthcare Pvt. Ltd.
Angel Space, Bldg. D-4, Gala No. 1 to 3 & 11 to 13 Ground Floor, 101 to 106 & 111 to 116 First Floor, 201 to 206 & 211 to 216 2nd Floor, Pimplas, Dist. Thane, Bhiwandi - 421 302, Maharashtra, India.

11. Details of permission or licence number
Refer Pack for Permission/License details

12. Date of revision
Version 2.0, dated 17/04/2025

For Product Complaints/Adverse events or Queries please write to
webmasterindia@abbott.com