Registration for KENYA

AMBRELLA-S (AMBROXOL HYDROCHLORIDE, LEVOSALBUTAMOL SULFATE & GUAIFENESIN SYRUP)

1. Name of the medicinal product

AMBRELLA-S (AMBROXOL HYDROCHLORIDE, LEVOSALBUTAMOL SULFATE & GUAIFENESIN SYRUP)

2. Qualitative and quantitative composition

Each 5 ml contains:

Ambroxol Hydrochloride BP….. .30 mg

Levosalbutamol Sulfate

Eq. to Levosalbutamol……..……1 mg

Guaifenesin BP……50 mg

Menthol Flavoured Syrupy Base……Q.S.

Colour: Tartrazine

3. Pharmaceutical form

Oral Liquid

A pale yellow colour syrup.

4. Clinical particulars

4.1 Therapeutic indications

Ambrella-S is a combination of respiratory medication used to treat asthma, cough with mucus, chronic obstructive pulmonary diseases (COPD) like bronchitis (inflammation of bronchial tubes), emphysema (shortness of breath), and upper respiratory tract infections. Asthma is a breathing problem in which airways narrow, swell, and produce extra mucus, leading to difficulty breathing. COPD is a chronic inflammatory lung disease caused by the obstructed airflow in the lungs. An upper respiratory tract infection is a contagious infection caused by a bacteria or virus infecting nose, throat, pharynx, larynx, and bronchi.

Ambrella-S consists of three medicines: Ambroxol (dilutes viscous cough), Guaifenesin and Salbutamol (widens narrowed airways). Salbutamol belongs to the class of drugs known as 'bronchodilators' that widen and relax the airways (bronchi) of the lungs. On the other hand, Ambroxol is an 'expectorant', which promotes the secretion of sputum/cough and a 'mucolytic agent' that makes sputum less viscous to make the breathing easier. Guaifenesin is also an 'expectorant'. It works by reducing the thickness or viscosity of bronchial secretions (phlegm) and increases mucus flow making it easier to cough.

Ambrella-S is available in oral syrup. Take the liquid/syrup with or without food in a dose and duration as advised by the doctor. Keep the liquid bottle away from direct sunlight. Shake the bottle well before use. Take Ambrella-Sregularly at a fixed time. Your doctor will decide the dose and duration of the course based on the severity of your disease. Do not stop taking Ambrella-S on your own until the doctor advised you to do so.

4.2 Posology and method of administration

13 - 18 years (Adolescent)
Disease: Asthma
Before or After Meal: Either
Single Maximum Dose: 5 ml
Dosage Route: Oral
Frequency: 3 daily
Course Duration: 7 days
Special Instructions: strength 1 mg levosalbutamol, 50 mg guaifenesin and 30 mg ambroxol in 5 ml

2 - 12 years (Child)
Disease: Asthma
Before or After Meal: Either
Single Maximum Dose: 2.5 ml
Dosage Route: Oral
Frequency: 3 daily
Course Duration: 7 days
Special Instructions: strength 1 mg levosalbutamol, 50 mg guaifenesin and 30 mg ambroxol in 5 ml, below 6 years old can take 1.25 ml 3 times daily

Adult
Disease: Asthma
Before or After Meal: Either
Single Maximum Dose: 2.5 ml
Dosage Route: Oral
Frequency: 3 daily
Course Duration: 7 days
Special Instructions: strength 1 mg levosalbutamol, 50 mg guaifenesin and 30 mg ambroxol in 5 ml

Geriatric
Disease: Asthma
Before or After Meal: Either
Single Maximum Dose: 5 ml
Dosage Route: Oral
Frequency: 3 daily
Course Duration: 7 days
Special Instructions: strength 1 mg levosalbutamol, 50 mg guaifenesin and 30 mg ambroxol in 5 ml

4.3 Contraindications
Ambrella-S 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
General

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 maynot be adequate to control asthma in many patients. Early consideration should be given to addinganti-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.

Guaiphenesin

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, Ambrella-S 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 StevensJohnson 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.

Ambrella-S Syrup should be used with caution in patients with diabetes mellitus, serious cardiovascular disorders, hypertension, hyperthyroidism and peptic ulcers.

4.5 Interaction with other medicinal products and other forms of interaction

Drug Interactions

<u>Levosalbutamol Sulphate</u>

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-potassiu- -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 Fertility, pregnancy and lactation

Pregnancy

Ambrella-S may be unsafe to use during pregnancy since it may show harmful effects on the developing baby. Consult your doctor before using Ambrella-S, if you are pregnant or planning to conceive.

Breast-feeding

There is limited data on how Ambrella-S affects breastfeeding. Please consult your doctor before starting Ambrella-S.

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

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 Pharmacodynamic properties

Levosalbutamol Sulphate

Levosalbutamol sulphate is a single-isomer beta2 -agonist that differs from racemic salbutamol by elimination of (S)-salbutamol. Levosalbutamol is an effective bronchodilator whose primary mechanism of action is unimpeded by (S)-salbutamol. Therefore, when compared with racemic salbutamol, clinically comparable bronchodilation can be achieved with doses that substantially lessen beta-mediated side effects.

Activation of beta2 -adrenergic receptors on airway smooth muscle leads to the activation of 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 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 clinical relevance of these findings is still unknown.

5.2 Pharmacokinetic properties

Levosalbutamol Sulphate

Absorption

Whether administered alone or as the racemate, salbutamol enantiomers are well absorbed from the gastrointestinal tract and time to maximum drug concentration (tmax) values ranges 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 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 Cmax was approximately 1.4 ug/mL, with Tmax 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 t½ 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.

5.3 Preclinical safety data
Animal Toxicology or Pharmacology

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/Subchronic 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 Tumourigenic 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 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 admixturefor 105 and 116 weeks, respectively.

Reproductive Toxicity
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 wasnot 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.

6. Pharmaceutical particulars

6.1 List of excipients
As per dossier

6.2 Incompatibilities
Not applicable

6.3 Shelf life
3 years

6.4 Special precautions for storage
Store below 30ºC protected from sunlight and moisture.

6.5 Nature and contents of container
100 ml PET bottle placed in carton with an insert.

6.6 Special precautions for disposal and other handling
No special requirements for disposal.

7. Manufactured By

LEXINE TECHNOCHEM PVT. LTD.