SUMMARY OF PRODUCT CHARACTERISTICS

1. **Name of the Medicinal Product**

Product Name: EASCOF-LS

Levosalbutamol Sulphate, Ambroxol Hydrochloride and Guaiphenesin Syrup

2. **Qualitative and quantitative composition:**

Each 5 ml contains:

Levosalbutamol Sulphate

Equivalent to Levosalbutamol ……. 1 mg

Ambroxol Hydrochloride BP……. 30 mg

Guaiphenesin BP…… 50 mg

Colour: Ponceau 4 R

Excipients with known effect: - Methyl Paraben, Propyl Paraben, Propylene Glycol, Colour Ponceau 4 R

For a full list of excipients, see section 6.1.

3. **Pharmaceutical form:**

Syrup for Oral use

Visual description of finished product: Clear dark pink coloured solution having mixed flavours of strawberry, raspberry and menthol.

4.Clinical particulars:

4.1 Therapeutic indications:

In management of cough associated with

Bronchial Asthma

Bronchitis

Chronic obstructive pulmonary disease (COPD)

Respiratory tract Infection (RTI)

4.2 Posology and method of administration

Adults and adolescents above 11 years: Syrup: 5-10 ml three times daily

Children 6 to 11 years: Syrup: 5 ml three times daily.

4.3 Contraindications

Hypersensitivity to any of the components of the formulation. It should not be used in patients with preexisting ischaemic heart disease or those patients with significant risk factors for ischaemic heart disease.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Levosalbutamol: Potentially serious hypokalemia may result from ß2-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. Levosalbutamol should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias or hypertension.

Ambroxol: Care to be taken to avoid contact with eye, skin, serious ingestion or inhalation.

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.

4.5 Interaction with other medicinal products and other forms of interaction

Levosalbutamol:

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.

Diuretics:

Diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists. Hence, caution is advised in the coadministration of beta agonists with non-potassium sparing diuretics.

Monoamine Oxidase Inhibitors or Tricyclic Antidepressants:

Levosalbutamol should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of levosalbutamol on the vascular system may be potentiated.

Ambroxol: No data available.

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).

Others:

Ambroxol hydrochloride and Guaiphenesin Expectorant should be used with caution in patients with diabetes mellitus, serious cardiovascular disorders, hypertension, hyperthyroidism and peptic ulcers.

4.6 Pregnancy and lactation

Levosalbutamol:

Caution should be exercised when oral levosalbutamol is administered to a nursing woman.

Ambroxol and Guaiphenesin: Pregnancy However, there are no adequate and well-controlled studies of this combination in pregnant women.

Hence this combination should be administered with caution in pregnancy.

Lactation: It is not known whether this combination is secreted in breast milk.

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 hand) and muscle cramps may occur due to levosalbutamol this may affects ability to drive and use of machines.

4.8 Undesirable effects

Levosalbutamol:

The most frequent side effects are 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.

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.

Guaiphenesin:

Side effects resulting from guaifenesin administration are very rare. Guaiphenesin has occasionally been reported to cause gastro-intestinal discomfort, nausea and vomiting, particularly in very high doses. Also, hypersensitivity reactions may occur.

4.9 Overdose

Levosalbutamol:

The expected symptoms with overdosage are tachycardia, nervousness, headache, tremor, nausea, dizziness, fatigue and sleeplessness. Hypokalaemia also may occur. Treatment consists of discontinuation of oral levosalbutamol together with appropriate symptomatic therapy. In the event of serious poisoning, the stomach should be emptied and, if necessary, a beta- blocker administered with caution in patients with a history of bronchospasm.

Ambroxol:

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 metabolised and excreted in the urine. Patients should be kept under observation and treated symptomatically.

5. Pharmacological Particulars

5.1 Pharmacodynamic properties

Levosalbutamol:

Levosalbutamol is a single isomer beta2-agonist that differs from racemic salbutamol by elimination of (S)-salbutamol. Levosalbutamol is an effective bronchodilator whose primary mechanism of action is unimpeded by (S)- salbutamol. Therefore, when compared with racemic salbutamol, clinically comparable bronchodilation can be achieved with doses that substantially lessen beta-mediated side effects. Activation of beta2-adrenergic receptors on airway smooth muscle leads to the activation of 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:

Ambroxol (group of benzilamides) belongs to secretolitical and secretomotoric medicinal products. It possesses expressed expectorant effect. Mechanism of action of the medicinal product is stipulated by stimulation of serous cells of tonsils of bronchial tubes' mucous membrane, increasing of mucous secretion content and changing of correlation of serous and mucous components of phlegm, breached under pathological processes in lungs. Under this hydrolyzing ferments activate and releasing of lysosomes from Clark's cells strengthens, that causes decreasing of viscosity of phlegm. Ambroxol increases content of surfactant in lungs, which is dealt with strengthening of synthesis of the last and secretion in alveolar pneumocytes, and also with breach of its disintegration. The medicinal product increases mucociliar transport of phlegm. It suppresses coughing insignificantly. Ambroxol well penetrates through the placenta barrier, improving synthesis of surfactants during uterine life of foetus, and also it has an ability to warn syndrome of insufficient breathing in newborn.

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.

5.2 Pharmacokinetic properties

Levosalbutamol: Enantioselective Disposition of (R, S)-Salbutamol: Racemic salbutamol is metabolized by sulphotranferase 1A3 (SULT1A3) to an inactive metabolite in human tissues. However (R)-salbutamol is sulphated eightfold faster than (S)-salbutamol because of its higher binding affinity for the enzyme.

Drug	AUC	Cmax	Tmax
(R, S)- Salbutamol	(ng.mL-1.min-1)	(ng.mL-1)	(min)
(R)-Salbutamol	812	3.49	106
(S)-Salbutamol 5	5,230	23.16	111

Pharmacokinetic parameters were based on assay of plasma from 12 healthy men after a single oral dose of (R, S)-salbutamol. Following oral administration of 10 mg (R, S)-salbutamol, the median peak plasma concentration of (R)- salbutamol of 3.49 ng/mL was significantly less than the value of (S)- salbutamol of 23.16 ng/mL. A similar study reported the ratio of AUCs for (S)- and (R)-salbutamol plasma concentrations to be about 8:1 (suggesting stereoselective metabolism of (R)- salbutamol). These observations indicate very efficient removal of the therapeutically beneficial (R)-enantiomer during (R, S)-salbutamol therapy, exposing the body to higher concentrations of the (S)-enantiomer for prolonged periods. In view of the potential opposing effects of (S)-salbutamol, it seems logical to remove this enantiomer from the currently used racemate to obtain safer bronchodilator therapy. On administration of racemic salbutamol, patients receive (R)- and (S)- salbutamol in equal amounts but are exposed to much greater amounts of the (S)-isomer for a prolonged period. Levosalbutamol appears to be stereo chemically stable in vivo and does not appear to interconvert metabolically to (S)-salbutamol.

Ambroxol:

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

Distribution: The distribution half-life of ambroxol is around 1.3 hours.

Metabolism: 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.

Guaiphenesin:

Absorption: Guaiphenesin is well absorbed from the gastro-intestinal tract following oral administration, although limited information regarding its pharmacokinetics is available.

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.

5.3 Preclinical safety data

Non-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction.

6. Pharmaceutical particulars

6.1 List of excipients:

Neotame
Sucralose
Sodium Citrate
EDTA Sodium
Glycerin
Sorbitol Solution 70% (Non-Crystallising)
Methyl Paraben
Propyl Paraben
Propylene Glycol
Colour Ponceau 4 R
Flavour Strawberry 14207 (OROR)

Flavour Ecocool MP (C81D00001) Ideal Cures

Flavour Raspberry IF- 1389 (Sensient)

Purified Water

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store in a dry place below 30°C. Protect from light.

Keep out of reach of Children. Shake well before use.

6.5 Nature and contents of container

100 ml Pink Transparent Round Pet Bottle in one carton along with its pack insert.

6.6 Special precautions for disposal and other handling

Not Applicable

7. Marketing authorization holder

Cachet Pharmaceuticals Pvt. Ltd

Address: 415, Shah Nahar, Worli,

Mumbai 400 018. India.

Phone No. Office +91-22-40829991

Email: - regulatory@cachetpharma.com

8. Marketing authorization number(s)

06940/08135/NMR/2020

9. Date of first authorization/renewal of the authorization

09/12/2021

10. Date of revision of the text

01/07/2023