1. NAME OF THE MEDICINAL PRODUCT

PRESCUF SYRUP (AMBROXOL HYDROCHLORIDE, GUAIFENESIN & LEVOSALBUTAMOL SULPHATE SYRUP)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

BATCH QUANTITY (for 1000.0 Litre)

S. No.	Material Name	Each Dose (5 ml)	Overages If Any (%)	Quantity for 1000.0 Litre (10000 bottles)
1.	Ambroxol Hydrochloride B.P	30 mg	5	6.30 kg
2.	Levosalbutamol Sulphate I.H. equivalent to Levosalbutamol	1 mg	5	0.252 kg
3.	Guaiphenesin B.P.	50 mg	5	10.5 kg
4.	Sodium Methyl Hydroxybenzoate B.P. (Sodium Methylparaben)	-		1.8 kg
5.	Sodium Propyl Hydroxybenzoate B.P. (Sodium Propylparaben)	-		0.180 kg
6.	Sodium Benzoate B.P.	-		1.00 kg
7.	Aspartame B.P.	-		0.300 kg
8.	Sucrose B.P.	-		600.00 kg
9.	Arrow Gum I.H.	-		2.000 kg
10.	Sodium Citrate B.P.			3.000 kg
11.	Colour: Ponceau 4R I.H.	-		0.050 kg
12.	Flavour: Strawberry I.H.			4.000 kg
13.	Citric Acid B.P.	-		4.000 kg
14.	Menthol B.P.	-		0.200 kg
15.	Propylene Glycol B.P.	-		60.000 kg
16.	Di-sodium Edetate B.P.	-		1.000 kg
17.	Purified Water I.H.	-		q. s to make 1000 Liter

BP: British Pharmacopoeia

IP: Indian Pharmacopeia

3. PHARMACEUTICAL FORM

Syrup

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ambroxol + Levosalbutamol + Guaifenesin 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.

4.2 Posology and method of administration

Posology
The usual recommended dose of PRESCUF SYRUP in children is as under: 2-5 years : 2.5 ml twice daily
6-12 years : 5 ml twice daily
Adults : 10 ml twice daily

4.3 Contraindications

PRESCUF SYRUP is contraindicated in patients with hypersensitivity to any ingredient of the formulation.

4.4 Precautions

While treating cough as a symptom, it is important to make every effort to determine and treat appropriately the underlying cause, such as a specific infection.
Caution should be observed while prescribing PRESCUF SYRUP to children with hypertension, cardiovascular disease, uncontrolled juvenile diabetes mellitus, hyperthyroidism, seizures or in patients who are unusually hypersensitive to sympathomimetic amines.

4.5 Interaction with other medicinal products and other forms of interaction

Hypokalemia with high doses of ß2 -agonists may result in increased susceptibility to digitalis induced cardiac arrhythmias. Hypokalemia may be enhanced by concomitant administration of aminophylline or other xanthines, corticosteroids or by diuretic therapy.

Other sympathomimetic bronchodilators or epinephrine should not be used concomitantly with salbutamol, since their combined effect on the cardiovascular system may be deleterious to the patient.
Salbutamol should be administered with caution in patients being treated with monoamine oxidase (MAO) inhibitors or tricyclic antidepressants, since the action of salbutamol on the vascular

system may be potentiated.

4.6 Fertility, pregnancy and lactation
Not Available

4.7 Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed. Possible side effects such as dizziness and visual disturbances may affect some patients' ability to drive and/or operate machinery.

4.8 Undesirable effects
The adverse reactions to Levosalbutamol are similar in nature to those of other sympathomimetic agents and include nervousness and tremor. The frequency of these side effects appears to diminish with continued therapy. Other commonly reported reactions include increased heart rate, palpitations, dizziness, headache, drowsiness, vomiting, nausea, sweating and muscle cramps. These reactions are generally transient and usually do not require treatment.

With ambroxol gastrointestinal side effects may occur occasionally and a transient rise in serum aminotransferase values has been reported.

Gastrointestinal discomfort has occasionally been reported with Guaiphenesin.

4.9 Overdose
No data are available in humans in regard to overdose by accidental or deliberate ingestion of the PRESCUF SYRUP.

5. PHARMACOLOGICAL PROPERTIES

5.1Pharmacodynamic properties
Pharmacotherapeutic group:
Mechanism of action
Levosalbutamol is a selective β-2-adrenoceptor agonist. At therapeutic doses it acts on the β-2-adrenoreceptors of bronchial muscle with little or no action on the α1-adrenoreceptors of cardiac muscle. Levosalbutamol (LEV) has approximately 2 fold greater affinity than racemic salbutamol (RAC) for the β2 adrenergic receptor and approximately 100 fold greater binding affinity than S-Salbutamol. Levosalbutamol stimulates the production of intracellular cyclic-AMP, enhancing the binding of intracellular calcium to the cell membrane and endoplasmic reticulum, resulting in bronchodilation. It also enhances mucociliary clearance.
Activation of the β-2-adrenoreceptors opens ATPase channels and drives potassium from the extracellular to the intracellular space. This both decreases extracellular hyperkalemia and increases intracellular potassium, so decreasing the chance of arrhythmia.
Ambroxol hydrochloride is a mucolytic agent, which liquefies thick, tenacious sputum. Ambroxol dissolves mucopolysaccharide fibers and thus reduces viscosity of sputum. It also improves mucocilliary clearance of secretions.

Guaiphenesin is an expectorant. It increases the output of sputum and bronchial secretions by reducing adhesiveness and surface tension. By increasing the volume of bronchial secretions, it reduces the viscosity of tenacious sputum. The increased flow of less viscid secretions also promotes ciliary action.

5.2 Pharmacokinetic properties

LEVOSALBUTAMOL
Absorption
Inhalation delivers the medication directly into the airways and lungs, thereby minimizing side effects because of reduced systemic absorption of the inhaled medications.

Volume of distribution
Not Available
Protein binding
plasma protein binding is relatively low.

Metabolism
Pure (R)-salbutamol formulation known as levosalbutamol is metabolised up to 12 times faster than (S)-salbutamol by intestine.

Route of elimination
excreted into the urine.

AMMBROXOL

Absorption
Rapid and almost complete.

Protein binding
Approximately 90%

GUAIPHENESIN

Absorption
Studies have shown that guaifenesin is well absorbed from and along the gastrointestinal tract after oral administration 2,10,7.

Volume of distribution
The geometric mean apparent volume of distribution of guaifenesin determined in healthy adult subjects is 116L (CV=45.7%) 11.

Protein binding
Information regarding the protein binding of guaifenesin is not readily available or accessible.

Metabolism

After the oral administration of 400 mg guaifenesin, the agent experiences rapid hydrolysis (more than 60% of the dose hydrolyzed over a range of seven hours) with β-(2-methoxyphenoxy)-lactic acid found as the major urinary metabolite but no parent drug detectable in the urine 5,7. Moreover, it has been observed that guaifenesin also experiences both oxidation and demethylation 5. In particular, the medication is quickly metabolized hepatically by way of oxidation to β-(2-methoxyphenoxy)-lactic acid 5. Furthermore, guaifenesin is also demethylated by O-demethylase in liver microsomes to the point where about 40% of an administered dose is excreted as this metabolite in the urine within 3 hours 5. In fact, O-demethylase appears to be the primary enzyme for the metabolism of guaifenesin and the primary metabolites of the substance are β-(2-methoxyphenoxy)-lactic acid and the demethylated hydroxyguaifenesin, both of which are themselves inactive moieties 5.

Route of elimination
After administration, guaifenesin is metabolized and then largely excreted in the urine.

5.3 Preclinical safety data
The profile of the individual components is well established.
Animal studies have not shown teratogenic effect.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Unopened: 24 months
After the container is opened for the first time: 28 days

6.4 Special precautions for storage

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

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

100 ml syrup filled in bottle. Such 1 bottle is packed in a carton with inserts.

6.6 Special precautions for disposal <and other handling>

No special requirements.

7. <APPLICANT/MANUFACTURER>

ZEST PHARMA

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