1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

1. Name of the medicinal product

AMBROXOL HYDROCHLORIDE, SALBUTAMOL SULFATE, GUAIFENESIN SYRUP

2. Qualitative and quantitative composition

ACTIVE INGREDIENTS				
APPROVED NAME	SPECIFICATION OR REFERENCE TEXT	QTY/5 ML		% OVERAGES
		QTY/5 ML	%W/W	
Ambroxol Hydrochloride	BP	0.015 gm	0.300 %	0.00 %
Salbutamol Sulfate	BP	0.0014 gm	0.028 %	0.00 %
Guaifenesin	BP	0.050 gm	1.000 %	0.00 %
INACTIVE INGREDIENTS				
APPROVED NAME	SPECIFICATION OR REFERENCE TEXT	QTY/5 ML		REASON FOR INCLUSION
		QTY/5 ML	%W/W	
Sodium Propyl Paraben	BP	0.005 gm	0.100 %	Preservative
Menthol	BP	0.0005 gm	0.010 %	Cooling Agent
Demineral Water	INHOUSE	2.905 ml	58.100 %	Vehicle
Sucrose	BP	1.850 gm	37.000 %	Sweetener
Sodium Methyl Paraben	BP	0.010 gm	0.200 %	Preservative
Ponceau 4R red colour	INHOUSE	0.00005 gm	0.001 %	Colour
Glycerin	BP	0.150 ml	3.000 %	Humactant
Sucralose	BP	0.005 gm	0.100 %	Sweetener
Essence mix fruit	INHOUSE	0.0075 ml	0.150 %	Essence

3. Pharmaceutical form

Oral Solution

4. Clinical particulars

4.1 Therapeutic indications

Ambroxol Hydrochloride, Salbutamol Sulfate, Guaifenesin Syrup is a medicine that is used for the treatment of Bronchitis, Back Pain, Cough, Congestion, Common Cold, Breathing Illnesses and other conditions.

4.2 Posology and method of administration

Liquid: Adult: 5-10 mL 3-4 times a day.
Children >2 years: 5 mL 3-4 times a day.
Not recommended for children <2 years.

4.3 Contraindications

Ambroxol: There are no absolute contraindications but in patients with gastric ulceration relative caution should be observed.
Salbutamol: Hypersensitivity to the active substance salbutamol or to the excipients.
Guaifenesin: Hypersensitivity to the active substance guaifenesin or to the excipients.

4.4 Special warnings and precautions for use

Before using this drug, inform your doctor about your current list of medications, over the counter products (e.g. vitamins, herbal supplements, etc.), allergies, pre-existing diseases, and current health conditions (e.g. pregnancy, upcoming surgery, etc.). Some health conditions may make you more susceptible to the side-effects of the drug. Take as directed by your doctor or follow the direction printed on the product insert. Dosage is based on your condition. Tell your doctor if your condition persists or worsens. Important counseling points are listed below.

- Alcohol consumption
- Always keep the inhaler upright during the loading of the dose
- Always replace the inhaler cap after use
- Asthma
- Avoid taking drugs that suppress cough
- Breastfeeding

4.5 Interaction with other medicinal products and other forms of interaction

Ambroxol: Combination of ambroxol oral solution with cough suppressants can, due to suppressed cough reflex, cause serious obstruction of the airways.
Administration of ambroxol with antibiotics (amoxicillin, cefuroxim, and erythromycin) leads to increase of antibiotics concentrations in mucus.
No clinically relevant unfavourable interactions with other medications have been reported.
Salbutamol: Salbutamol and non-selective β – receptor blocking drugs should not usually be prescribed together. In patients with asthma administration of β – receptor blocking drugs is associated with a risk of severe bronchoconstriction.
Treatment with salbutamol can lead to hypokalaemia. This effect may be potentiated by the concomitant administration of other drugs, in particular xanthine derivatives, glucocorticoids, diuretics and cardiac glycosides (digoxin). Serum potassium levels should be monitored in these situations.
Tricyclic antidepressants may increase the risk of cardiovascular side effects.
Corticosteroids may increase the risk of hyperglycaemia.
Guaifenesin: If urine is collected within 24 hours of a dose of this product a metabolite of guaifenesin may cause a colour interference with laboratory determinations of urinary 5-hydroxyindoleacetic acid (5-HIAA) and vanillylmandelic acid (VMA).

4.6 Pregnancy and lactation

Ambroxol: Pregnancy: There are no adequate data from the use of ambroxol in pregnant women, especially in the first 28 weeks of pregnancy. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Clinical experience to date has shown no evidence of harmful effects on the foetus during pregnancy. 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.
Lactation: In animal studies, ambroxol is excreted in breast milk. As there are no adequate data from the use of ambroxol in breastfeeding women, ambroxol should be prescribed to breastfeeding women only after careful evaluation of risk and benefit.
Salbutamol: Based on preclinical studies and long-term clinical experience, salbutamol has not been shown to have any teratogenic effects. If the mother uses salbutamol during pregnancy, the pulse rate of the foetus may increase. Since salbutamol is passively excreted in breast milk, high doses may induce drug effect in the breast-fed infant.
Although salbutamol is considered the first line treatment to relieve bronchospasm in asthmatic pregnant women, use during pregnancy, especially in the first trimester, and lactation should only be considered once the benefits have been carefully weighed against the risks.
Guaifenesin: Pregnancy: There are no or limited amount of data from the use of Guaifenesin in pregnant women. Animal studies are insufficient with respect to reproductive toxicity. Insufficient information is available on the effects of administration of this product during human pregnancy. This product is not recommended during pregnancy and in women of childbearing potential not using contraception
Breastfeeding: Guaifenesin is excreted in breast milk in small amounts. There is insufficient information on the effects of Guaifenesin in newborns/infants. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from this product, taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.
Fertility: There is insufficient information available to determine whether guaifenesin has the potential to impair fertility.

4.7 Effects on ability to drive and use machines

Ambroxol: No studies on the effects on the ability to drive and use machines have been performed with ambroxol hydrochloride. On the basis of pharmacokinetic profile and reported adverse reactions the medicinal product has no or negligible influence on the ability to drive and use machines.
Salbutamol: None known
Guaifenesin: This product has no or negligible influence on the ability to drive or operate machinery.

4.8 Undesirable effects

The following is a list of possible side-effects that may occur from all constituting ingredients of Ambroxol Hydrochloride, Salbutamol Sulfate, Guaifenesin Syrup. This is not a comprehensive list. These side-effects are possible, but do not always occur. Some of the side-effects may be rare but

serious. Consult your doctor if you observe any of the following side-effects, especially if they do not go away.

- Stomach Pain
- Loose Motions
- Vomiting
- Itchy Skin Rash
- Hypersensitivity
- Urge To Vomit

4.9 Overdose

Ambroxol: Symptoms: Serious symptoms during overdosage with ambroxol were not recorded. Short-term restlessness and diarrhoea were most common. Ambroxol administered parenterally up to dose of 15 mg/kg/day and orally up to 25 mg/kg/day was well tolerated. According to the pre-clinical data in the case of extreme overdosage symptoms of sialorrhea, nausea, vomiting and hypotension can be expected.
Treatment: Acute measures, such as administration of an antiemetic and gastric lavage are not generally indicated as those symptoms are to be expected only in extreme cases of overdosing. Treatment of ambroxol overdose should be mainly symptomatic.
Salbutamol: Symptoms: The most common signs and symptoms of overdose with salbutamol are transient beta agonist pharmacologically mediated events, including tachycardia, tremor, hyperactivity and metabolic effects including hypokalaemia. Salbutamol overdose may lead to Hypokalaemia (abnormally low potassium concentration in the blood). Serum potassium levels should therefore be monitored. Lactic acidosis has been reported in association with high therapeutic doses as well as overdoses of short-acting beta-agonist therapy, therefore monitoring for elevated serum lactate and consequent metabolic acidosis (particularly if there is persistence or worsening of tachypnea despite resolution of other signs of bronchospasm such as wheezing) may be indicated in the setting of overdose. Nausea, vomiting and hyperglycaemia have been reported, predominantly in children and when salbutamol overdose has been taken via the oral route.
Treatment: The preferred antidote for overdose with salbutamol sulphate is a cardioselective beta-blocking agent, which should be used with caution in patients with a history of bronchospasm. Further management should be as clinically indicated or as recommended by the national poisons centre, where available.
Guaifenesin: Symptoms and signs: The effects of acute toxicity from guaifenesin may include gastro-intestinal discomfort, nausea and drowsiness. When taken in excess, guaifenesin may cause renal calculi.
Treatment: Treatment should be symptomatic and supportive.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Ambroxol: Pharmacotherapeutic group: Mucolytics, ATC code: R05CB06
Ambroxol, a metabolite of bromhexin, 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 defence mechanisms and resulting in

more productive cough. The pharmacological effect is exerted on mucus quality, ciliary function and the production of alveolar surfactant. Mucus quality: ambroxol stimulates the activity of serous glandular cells, clears granules of mucus that have already formed, normalizes secretion viscosity and finally regularizes the activity of the tubuloacinar glands in the respiratory tract. Ciliary function: ambroxol increases both the number of microvilli in the vibratile epithelium and the frequency of ciliary movements, with a resulting increase in the speed of transport of secretion produced, and finally normalizes respiratory tone, improving expectoration. Increase in surfactant production: ambroxol stimulates synthesis and release of surfactant by type II pneumocytes in alveolae and in small airways in foetal, as well as in adult lungs, thus ensuring the stability of the lung tissue, allowing correct bronchiolar and alveolar clearance and finally facilitating respiratory mechanics and encouraging gaseous exchanges. Those effects were observed in vitro as well in vivo in different animal species. In several pre-clinical experiments antioxidative effects of ambroxol were noted. Up to date no clinical relevance of this observation was confirmed.
Salbutamol: Broncholytic/antiasthmatic/ β2-sympathomimetic. ATC-Code: R03AC02.
Salbutamol is a selective beta2-adrenoceptor agonist. At therapeutic doses it acts on the beta2-adrenoceptors of bronchial muscle to provide bronchodilation. With its fast onset of action (within 5 minutes) it is particularly suitable for the management and prevention of attacks in asthma. Salbutamol has duration of action of 4 to 6 hours in most patients.
Guaifenesin: Pharmacotherapeutic Group: Cough and cold preparations, Expectorants. ATC Code: R05CA10.
Guaifenesin 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 in reflex 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 centres in the brain which in turn enhance respiratory fluid flow. Guaifenesin produces its expectorant action within 24 hours.

5.2 Pharmacokinetic properties

Ambroxol: The bioavailability of ambroxol has been evaluated in humans after the oral administration of the drug in healthy volunteers. Ambroxol is almost completely absorbed after oral administration. Tmax is 1-3 hours. It is extensively bound to plasma proteins (90%). Half-time of ambroxol in plasma is 7-12 hours. Sum of half-life of ambroxol and its metabolites in plasma is about 22 hours. Ambroxol crosses in the amniotic fluid and placenta, and is secreted in breast milk. Ambroxol is metabolized in the liver. Bioavailability of absorbed ambroxol is lowered by a third due to the first pass metabolism in the liver. About 90% of ambroxol and its metabolites are eliminated through the kidneys. Less than 10% of ambroxol is eliminated unchanged by the kidneys. Due to high protein binding and big distribution volume, as well as slow re-release from the tissues in blood dialysis or forced diuresis will be ineffective in elimination of ambroxol. In patients with severe hepatic impairment clearance of ambroxol lowers 20 – 40%. In patients with severe renal impairment accumulation of ambroxol metabolites is to be expected.
Salbutamol: Absorption and metabolism of salbutamol in lungs and gastrointestinal tract differ.
After inhalation, between 10 and 20 % of the active substance reaches the lower airways. The remainder is retained in the delivery system or is deposited in the oropharynx where it is swallowed. The fraction deposited in the airways is absorbed into the pulmonary tissues and

circulation, but is not metabolised by the lung. On reaching the systemic circulation it becomes accessible to hepatic metabolism and is excreted, primarily in the urine, as unchanged drug and as the phenolic sulfate.
The swallowed portion of an inhaled dose is absorbed from the gastrointestinal tract and undergoes considerable first-pass metabolism to the phenolic sulfate. Both unchanged drug and conjugate are excreted primarily in the urine. Approximately 90% of an oral dose is excreted in urine and 10% in faeces. Salbutamol administered intravenously has a half life of 4 to 6 hours and is cleared partly renally, and partly by metabolism to the inactive 4'-O-sulfate (phenolic sulfate) which is also excreted primarily in the urine. Most of a dose of salbutamol given intravenously, orally or by inhalation is excreted within 72 hours. Salbutamol is bound to plasma proteins to the extent of 10%.
Guaifenesin: Absorption: Guaifenesin is well absorbed from the gastro-intestinal tract following oral administration, although limited information is available on its pharmacokinetics. After the administration of 600 mg guaifenesin 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 guaifenesin or menthol in humans.
Metabolism and elimination: Guaifenesin 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.

5.3 Preclinical safety data

Ambroxol: 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.
Salbutamol: Preclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction. Effects seen in toxicity studies were related to the beta-adrenergic activity of salbutamol.
Guaifenesin: Preclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction. Effects seen in toxicity studies were related to the beta-adrenergic activity of Guaifenesin.

6. Pharmaceutical particulars

6.1 List of Excipients

- Sodium Propyl Paraben
- Menthol
- Demineral Water
- Sucrose
- Sodium Methyl Paraben
- Ponceau 4R red colour
- Glycerin
- Sucralose

- Essence mix fruit
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6.2 Incompatibilities

None known.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store in a dry place at a temperature below 30°C.

6.5 Nature and contents of container

100 ml Amber colour bottle pack, packed in printed and laminated carton.

6.6 Special precautions for disposal and other handling

Not applicable.

7. Marketing authorisation holder

West Coast Pharmaceutical Works Ltd, Ahmedabad

8. Marketing authorisation number(s)

Not applicable.

9. Date of first authorisation/renewal of the authorisation

Not applicable.

10. Date of revision of the text

February, 2018