1.3.1 Summary of product characteristics

1. Name of the medicinal product

BROZELIN (Ambroxol, Salbutamol & Guaifenesin Expectorant)

2. Qualitative and quantitative composition

Each 5 ml contains:

Ambroxol Hydrochloride BP 30 mg

Salbutamol Sulfate BP

Equivalent to Salbutamol 2 mg

Guaifenesin BP 50 mg

Qualitative

Excipients	Specification	Functional Category
Ambroxol Hydrochloride	BP	Mucolytic agent
Salbutamol Sulfate	BP	β2-adrenergic receptor agonist
Guaifenesin	BP	Expectorant
Menthol	USP	Cooling agent
Methyl hydroxybenzoate	BP	Antimicrobial preservative
Propyl hydroxybenzoate	BP	Antimicrobial preservative
Sodium benzoate	BP	Antimicrobial preservative
Disodium edetate	BP	Chelating agent
Sucrose	BP	Sweetening agent
Sorbitol 70% (Non, crystallising)	BP	Plasticizer
Glycerol	BP	Humectant
Propylene glycol	BP	Solvent
Citric acid anhydrous	BP	Buffering agent
Sunset yellow supra	IH	Colouring Agent
Ess.Sweet orange	IH	Flavouring agent
Ess.Bitter mask No.1	IH	Flavouring agent
Purified water	BP	Solvent

Quantitative Composition

S. No.	Ingredients	Label claim (mg)	Overage in %	Added/ (ml)	Added kg/ Batch	Specifi -cation	Function
Active Ingredients:							
1.	Ambroxol Hydrochloride	30mg	2%	30.600	6.120	BP	Mucolytic agent
2.	Salbutamol Sulfate	2mg	2%	2.458	0.491	BP	β2-adrenergic receptor agonist
3.	Guaifenesin	50mg	2%	51.000	10.200	BP	Expectorant
In Active Ingredients:							
4.	Menthol	1mg	--	1.050	0.210	USP	Cooling agent
5	Methyl hydroxybenzoate	---	--	5.000	1.000	BP	Antimicrobial preservative
6.	Propyl hydroxybenzoate	---	--	0.500	0.100	BP	Antimicrobial preservative
7	Sodium benzoate	---	--	2.500	0.500	BP	Antimicrobial preservative
8	Disodium edetate	---	--	2.500	0.500	BP	Chelating agent
9	Sucrose	---	--	3000.00	600.000	BP	Sweetening agent
10	Sorbitol 70% (Non, crystallising)	---	--	500.000	100.000	BP	Plasticizer
11	Glycerol	---	--	350.000	70.000	BP	Humectant
12	Propylene glycol	---	--	450.000	90.000	BP	Solvent
13	Citric acid anhydrous	---	--	1.150	0.230	BP	Buffering agent
14	Sunset yellow supra	---	--	0.250	0.050	IH	Colouring Agent
15	Ess.Sweet orange	---	--	35.000	7.000	IH	Flavouring agent
16	Ess.Bitter mask No.1	---	--	0.025	5.000	IH	Flavouring agent
17	Purified water	---	---	q.s	q.s	BP	Solvent

Abbreviation:

USP : United States Pharmacopoeia

BP : British Pharmacopoeia

IH : In-House

* - Qty of Ambroxol Hydrochloride, Salbutamol sulfate and Guaifenesin, shall be added based on the assay and water content

3. Pharmaceutical Form

Orange coloured, flavoured clear viscous syrupy liquid.

4 Clinical particulars

4.1 Therapeutic indications

In productive cough associated with, asthmatic bronchitis, bronchospasm, chronic obstructive pulmonary spasm and smokers cough.

4.2 Posology and method of administration

Adults : 5-l0 ml 3 or 4 times daily

Children : Under 2 years: Not recommended

2-6 years : 2.5ml 2 to 3 times daily

6-12 years : 5 ml 2 to 3 times daily

Above 12 years: 10 ml 2 times daily

If your symptoms persist, see your doctor

4.3 Contraindications

Hypersensitivity to any of the ingredients, cardiovascular disease, hyperthyroidism, pregnancy and lactation, patients with acute porphyria.

4.4 Special warnings and precautions for use

Guaiphenesin should not be taken for persistent cough eg, occurs with smoking, emphysema or where cough is accompanied by excessive secretions except under the advice and supervision of a doctor. A persistent cough may be a sign of a serious condition.

4.5 Interaction with other medicinal products and other forms of interaction

Caution should be exercised during use with anaesthetic agents such as chloroform, cyclopropane, halothane and other halogenated agents.

The effects of this product may be altered by guanethidine, reserpine, methyldopa, tricyclic antidepressants.

Salbutamol oral preparations and beta-blocking drugs, such as propranolol should not usually be prescribed together.

Salbutamol is not contraindicated in patients under treatment with monoamine oxidase inhibitors (MAOI's)

Ambroxol is not recommended for co-administration with expectorants (e.g, codeine), Cough reflex depression may occur due to excessive accumulation of sputum and threatening obstruction of respiratory tract. Clinically significant adverse interactions with other drugs have not been observed. The drug can be used simultaneously with antibiotics such as amoxicillin, cefuroxime, erythromycin and doxycycline, antibiotics penetration into lung tissues and their efficacy increase.

4.6 Fertility, pregnancy and lactation

Pregnancy

Caution is advised when used during pregnancy. Use during the first trimester of pregnancy is not recommended.

Should not be taken during lactation.

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. An effect on the ability to drive and operate machines is unknown.

4.8 Undesirable effects

Gastrointestinal disturbances, headache, dry mouth and skin rashes have been reported. Fine tremor, nervous tension, peripheral vasodilatation, palpitation and tachycardia

4.9 Overdose

Ambroxol Hydrochloride

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

Excess repeat use of inhalations may produce adverse effects such as tachycardia, CNS stimulation, tremor, hypokalaemia and hyperglycaemia.

Treatment

Treatment consists of discontinuation of salbutamol together with appropriate symptomatic therapy. The preferred antidote for overdosage with salbutamol is a cardioselective beta-blocking agent, but beta-blocking drugs should be used with caution in patients with a history of bronchospasm. Hypokalaemia may occur following overdose with salbutamol. Serum potassium levels should be monitored. If hypokalaemia occurs potassium replacement via the

oral route should be given. In patients with severe hypokalaemia intravenous replacement may be necessary.

Guaiphenesin

Symptoms

The symptoms and signs of overdose may include gastro-intestinal discomfort, nausea and drowsiness.

Treatment

Treatment should be symptomatic and supportive

5. Pharmacological properties

5.1 Pharmacodynamic properties

Ambroxol HCl is a mucolytic drug administered when there is excessive and tenacious sputum.

Salbutamol sulphate is a sympathomimetic drug administered during bronchospasm in bronchial asthma and chronic bronchitis. Also administered for prophylaxis against bronchial asthma

Guaiphenesin is a directly acting expectorant administered to increase the volume and reduce viscosity of bronchial secretion and hence coughing facilitates the removal.

5.2 Pharmacokinetic properties

Ambroxol Hydrochloride

Oral bioavailability is approx. 60% owing to the first-pass effect. Plasma concentrations are in a linear relationship to the dose. Peak plasma levels are attained after 0.5 to 3 hours. Plasma protein binding is around 90% in the therapeutic range. After oral, intravenous and intramuscular administration ambroxol is distributed swiftly and extensively from the blood into the tissues. The highest active ingredient concentrations are measured in the lung. Metabolism Studies in human liver microsomes showed that CYP3A4 is the predominant isoform for ambroxol metabolism. Otherwise ambroxol is metabolised in the liver mainly by conjugation. Around 30% of an oral dose is eliminated via the first-pass effect. The terminal half-life is about 10 hours. Total clearance is in the region of 660 ml/min, and renal clearance is 8% of total clearance.

Salbutamol

Readily absorbed from the gastro-intestinal tract and is subject to first pass metabolism in the liver. Peak plasma concentrations occur within one to four hours after oral administration. After multiple oral doses of salbutamol 4mg four times a day, steady-state plasma concentrations are obtained after 3 days. About half is excreted in the urine as an inactive

sulphate conjugate following oral administration. The bioavailability of orally administered salbutamol is about 50%.

Guaiphenesin

Guaiphenesin is readily absorbed. The half-life is 1 hour, renal excretion; major urinary metabolite is beta-2-(methoxyphenoxy) lactic acid

5.3 Preclinical safety data

Ambroxol Hydrochloride

Ambroxol HCl was well tolerated in single-dose toxicity studies (mouse, rat, rabbit and dog) following oral and parenteral administration. Oral repeat-dose toxicity studies in the mouse, rat, rabbit and dog up to 78 weeks showed low toxicity. Following high level there were clinical signs of toxicity such as body weight decrease and CNS disorders including decreased motoric activity, ataxia and convulsions. All adverse effects were reversible without any evidence for progression. There were no consistent treatment-related effects on clinical chemistry, cardiovascular function, ophthalmoscopy, hematology, urinalysis, macroscopy and histopathology. In none of the studies, any toxicological target organs were identified. Based on a comprehensive battery of in vitro and in vivo studies, ambroxol HCl is free of any genotoxic potential. Oral doses of ambroxol HCl in rats did not impair male and female fertility or early embryonic development. There was no evidence for any teratogenic potential up to maternotoxic dose levels. Peri-and postnatal development including reproductive function was unaffected by oral exposure of rats to ambroxol HCl. There was no evidence for a treatment-related tumorigenic potential of ambroxol HCl in mice and rats.

Reference: http://mri.medagencies.org/download/BE_H_0181_003_PAR.pdf

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. The observed effects in the preclinical studies were related to the beta-adrenergic activity of salbutamol.

In common with other potent selective β2-receptor 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, 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 fetal 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. 78 times the maximum

human oral dose) have shown fetuses 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.

Reference: https://www.medicines.org.uk/emc/medicine/22405

Guaiphenesin

Mutagenicity

There is insufficient information available to determine whether Guaiphenesin has mutagenic potential.

Carcinogenicity

There is insufficient information available to determine whether Guaiphenesin has carcinogenic potential.

Teratogenicity

There is insufficient information available to determine whether Guaiphenesin has teratogenic potential.

Fertility

There is insufficient information available to determine whether Guaiphenesin has the potential to impair fertility

Reference: https://www.medicines.org.uk/emc/medicine/7082

6. Pharmaceutical particulars

6.1 List of excipients

Excipients	Specification	Functional Category
Menthol	USP	Cooling agent
Methyl hydroxybenzoate	BP	Antimicrobial preservative
Propyl hydroxybenzoate	BP	Antimicrobial preservative
Sodium benzoate	BP	Antimicrobial preservative
Disodium edetate	BP	Chelating agent
Sucrose	BP	Sweetening agent
Sorbitol 70% (Non, crystallising)	BP	Plasticizer
Glycerol	BP	Humectant
Propylene glycol	BP	Solvent
Citric acid anhydrous	BP	Buffering agent
Sunset yellow supra	IH	Colouring Agent
Ess.Sweet orange	IH	Flavouring agent
Ess.Bitter mask No.1	IH	Flavouring agent
Purified water	BP	Solvent

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store below 30°C. Protect from light

Keep out of reach of children.

6.5 Nature and contents of container

BROZELIN (Ambroxol, Salbutamol & Guaifenesin Expectorant) are packaged into 100ml Amber colour glass bottle

6.6 Special Precautions for Disposal and Other Handling

Not applicable.

6.7 Marketing authorization holder

Prisma Pharma FZE, P.O.Box 17269, Jebel Ali Free Zone, Dubai, U.A.E.

6.8 Marketing authorization Number

6.9 Date of first authorization/renewal of the authorization

6.10 Date of revision of the text-Nil