SUMMARY OF PRODUCT CHARACTERISTICS

1. Name Of The Medicinal Product

Product Name: BROZELIN (Ambroxol Hydrochloride, Salbutamol and Guaifenesin syrup**)**

1.1 Composition:

Each 5ml contains:

Ambroxol hydrochloride	BP	30mg
Salbutamol Sulfate		
Equivalent to Salbutamol	BP	2mg
Guaifenesin	BP	50mg
Menthol	USP	1mg

1.2 Pharmaceutical dosage form and route of administration :

Cough Syrup and Oral

2. Qualitative and quantitative composition

2. 1 Qualitative composition

S. No.	Ingredients	Specification	Function
1.	Ambroxol Hydrochloride	BP	Mucolytic agent
2.	Salbutamol sulfate equivalent to Salbutamol	BP	β2-adrenergic receptor agonist
3.	Guaifenesin	BP	Expectorant
4.	Menthol	USP	Cooling agent
5	Sucrose	BP	Sweetening agent
6.	Sorbitol	BP	Sweetening agent
7	Glycerol	BP	Sweetening agent
8	Propylene glycol	BP	Solvent
9	Sodium Benzoate	BP	Preservative
10	Bronopol	BP	Preservative
11	Disodium Edetate	BP	Chelating agent
12	Anhydrous Citric acid	BP	Buffering agent

S. No.	Ingredients	Specification	Function
13	Sunset Yellow supra	IH	Colouring Agent
14	Sweet Orange flavour	IH	Flavouring agent
15	Bitter mask flavour	IH	Flavouring agent
16	Purified water	BP	Solvent

2.2 Quantitative composition

Batch Size: 3000 Litres

S. No.	Ingredients	Label claim (mg)	Overage in %	Added/ (ml)	Added kg/ Batch
1.	Ambroxol Hydrochloride	30mg	2%	30.60	18.36
2.	Salbutamol sulfate equivalent to Salbutamol	2mg	2%	2.45	1.47
3.	Guaifenesin	50mg	2%	51.00	30.60
4.	Menthol	---	5%	1.05	0.63
5	Sucrose	---	--	3000.00	1800
6.	Sorbitol	---	--	500.00	300
7	Glycerol	---	--	350.00	210
8	Propylene glycol	---	--	450.00	270
9	Sodium Benzoate	---	--	2.50	1.50
10	Bronopol	---	--	0.25	0.15
11	Disodium Edetate	---	--	2.50	1.50
12	Anhydrous Citric acid	---	--	1.15	0.69
13	Sunset Yellow supra	---	--	0.25	0.15
14	Sweet Orange flavour	---	--	35.00	21.00
15	Bitter mask flavour	---	--	25.00	15.00
16	Purified water	---	--	q.s	-

*** -** Qty of Ambroxol Hydrochloride, Salbutamol (as sulfate), Guaifenesin, shall be dispensed based on Assay and LOD

Abbreviation:

USP : United States Pharmacopoeia

BP : British Pharmacopoeia

IH : In-House

3. Pharmaceutical form

Orange coloured clear 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

Guaifenesin 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 interactions:

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 Pregnancy and lactation

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.

Guaifenesin

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

Name of API	Pharmacotherapeutic group	Anatomical Therapeutic Chemical (ATC) Code
Ambroxol Hydrochloride	Mucolytics	R05CB06
Salbutamol Sulfate	Selective beta-2-adrenoreceptor agonists	R03CC02
Guaifenesin	Expectorants	R05CA03

Ambroxol HCl is a mucolytic drug administered when there is excessive and tenacious sputum. Salbutamol sulfate is a sympathomimetic drug administered during bronchospasm in bronchial asthma and chronic bronchitis. Also administered for prophylaxis against bronchial asthma Guaifenesin 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 sulfate conjugate following oral administration. The bioavailability of orally administered salbutamol is about 50%.

Guaifenesin

Guaifenesin 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

Guaifenesin

Mutagenicity

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

Carcinogenicity

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

Teratogenicity

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

Fertility

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

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

6. Pharmaceutical particulars

6.1 List of excipients

S. No	Ingredients	Specification	Function
1.	Menthol	USP	Cooling agent
2.	Sucrose	BP	Sweetening agent
3.	Sorbitol	BP	Sweetening agent
4.	Glycerol	BP	Sweetening agent
5.	Propylene glycol	BP	Solvent
6.	Sodium Benzoate	BP	Preservative
7.	Bronopol	BP	Preservative
8.	Disodium Edetate	BP	Chelating agent
9.	Anhydrous Citric acid	BP	Buffering agent
10.	Sunset Yellow supra	IH	Colouring Agent
11.	Sweet Orange flavour	IH	Flavouring agent
12.	Bitter mask flavour	IH	Flavouring agent
13.	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

a) **Type of package -** Amber colour glass bottle Pack

b) **Nature and packaging material -** 100ml Amber colour glass bottle

6.6 Instructions for use handling for disposal

No special requirements.

7. Marketing Authorisation Holder

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Manufactured in India by

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8. Number(s) in the National Register of Finished Pharmaceutical Products

9. Date of First Authorisation/Renewal of the Authorisation

10. Date of Revision of the text –Nil