Kofarest™ SYRUP

1. Generic Name

Terbutaline, Ambroxol HCl, Guaiphenesin, Menthol

2. Qualitative and Quantitative composition

Terbutaline.....2.5mg

Ambroxol HCl.....30mg

Guaiphenesin.....100mg

Menthol.....5mg

3. Dosage form and strength

Oral syrup containing Terbutaline 2.5mg, Ambroxol HCl 30mg,Guaiphenesin 100mg

4. Clinical particulars

4.1 Therapeutic indication

Kofarest syrup is indicated for the treatment of productive cough when associated with bronchospasm in conditions such as bronchitis, bronchial asthma, chronic obstructive pulmonary disease (COPD), bronchiectasis and emphysema.

4.2 Posology and method of administration

Recommended oral dose for Kofarest Syrup is 10ml 3-4 times a day or as directed by physician.

4.3 Contraindication

Kofarest Syrup is contraindicated in patients with hypersensitivity to any ingredient of the formulation.

4.4 Special warnings and precautions for use

- 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 Kofarest syrup to adults and children with hypertension, cardiovascular disease, uncontrolled diabetes mellitus, hyperthyroidism, seizures or in patients who are unusually hypersensitive to sympathomimetic amines.
- Since mucolytics, such as Ambroxol, may disrupt the gastric mucosal barrier, Kofarest Syrup should be used with care in patients with a history of peptic ulceration.

4.5 Drug interactions

- 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.
- Terbutaline should be administered with caution in patients being treated with monoamine oxidase (NAO) inhibitors or tricyclic antidepressants, since the action of Terbutaline on the vascular system may be potentiated.

4.6 Use in special population

- Pediatric: Safe in children.
- Geriatric: Clinical studies of did not include sufficient numbers of subjects aged 65 years and older to determine whether they respond differently from younger subjects. If clinically warranted due to insufficient bronchodilator response, the dose of may be increased in elderly patients as tolerated, in conjunction with frequent clinical and laboratory monitoring, to the maximum recommended daily dose.
- Liver impairment: Use with caution.
- Renal failure: Use with caution.

- Pregnancy and lactation: Safety of Kofarest Syrup has not been studied in pregnancy and lactation. Therefore, probable benefits should be weighed against possible risks, before prescribing.

4.7 Effects on ability to drive and use machine

Patients should be cautioned against engaging in activities requiring complete mental alertness, and motor coordination such as operating machinery until their response to Kofarest Syrup is known.

4.8 Undesirable effects

- The adverse reactions to Terbutaline 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 amino transferase values has been reported.
- Gastrointestinal discomfort has occasionally been reported with Guaiphenesin.

4.9 Overdose

There is limited experience of overdose with Kofarest Syrup. Initiate general symptomatic and supportive measures in all cases of overdosages where necessary.

5. Pharmacological properties

5.1 Mechanism of action

Terbutaline is a relatively selective beta2-adrenergic bronchodilator that has little or no effect on alpha-adrenergic receptors. The drug has exerts a preferential effect on beta2-adrenergic receptors but stimulates beta-adrenergic receptors less selectively than relatively selective beta2-agonists. Terbutaline appears to have a greater stimulating effect on beta-receptors of the bronchial, vascular, and uterine smooth muscles (beta2 receptors)

than on the beta-receptors of the heart (beta1 receptors). This drug relaxes smooth muscle and inhibits uterine contractions, but may also cause some cardiostimulatory effects and CNS stimulation.

Guaiphenesin is an expectorant which increases the output of phlegm (sputum) and bronchial secretions by reducing adhesiveness and surface tension. The increased flow of less viscous secretions promotes ciliary action and changes a dry, unproductive cough to one that is more productive and less frequent. By reducing the viscosity and adhesiveness of secretions, Guaiphenesin increases the efficacy of the mucociliary mechanism in removing accumulated secretions from the upper and lower airway.

5.2 Pharmacodynamic properties

The pharmacologic effects of terbutaline are at least in part attributable to stimulation through beta-adrenergic receptors of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic- 3',5'- adenosine monophosphate (c-AMP). Increased c-AMP levels are associated with relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

Ambroxol is a mucolytic agent. Excessive Nitric oxide (NO) is associated with inflammatory and some other disturbances of airways function. NO enhances the activation of soluble guanylate cyclase and cGMP accumulation. Ambroxol has been shown to inhibit the NO-dependent activation of soluble guanylate cyclase. It is also possible that the inhibition of NO-dependent activation of soluble guanylate cyclase can suppress the excessive mucus secretion; therefore it lowers the phlegm viscosity and improves the mucociliary transport of bronchial secretions.

Guaiphenesin may act as an irritant to gastric vagal receptors, and recruit efferent parasympathetic reflexes that cause glandular exocytosis of a less viscous mucus mixture. Cough may be provoked. This combination may flush tenacious, congealed mucopurulent material from obstructed small airways and lead to a temporary improvement in dyspnea or the work of breathing.

Menthol has a cooling effect on the throat. It has been suggested that the benefits of menthol may be due to an effect on calcium channels of sensory nerves.

5.3 Pharmacokinetic properties

On inhalation of Terbutaline, less than 10% of the drug is absorbed from the airways. The remainder is swallowed where it is variably absorbed from the gastrointestinal tract. Fasting bioavailability after oral doses is reported to be about 14 to 15% and is reduced by food. Terbutaline undergoes extensive first-pass metabolism by sulfate (and some glucuronide) conjugation in the liver and the gut wall. It is excreted in the urine and faeces partly as the inactive sulfate conjugate and partly as unchanged Terbutaline, the ratio depending upon the route by which it is given. The terminal half-life after single and multiple dosing is reported to be between 16 and 20 hours. There is some placental transfer. Trace amounts are distributed into breast milk.

Guaiphenesin is well absorbed from the gastrointestinal tract. It is metabolised and then excreted in the urine.

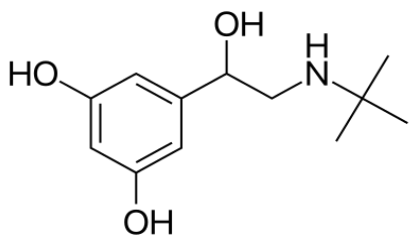
6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

NA.

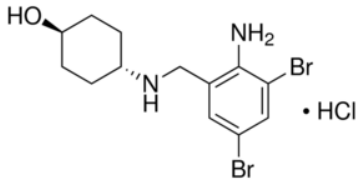
7. Description

Terbutaline is in a class of medications called beta agonists. Its chemical name is 5-[2-(tert-butylamino)-1-hydroxyethyl]benzene-1,3-diol; sulfuric acid and its chemical structure is:



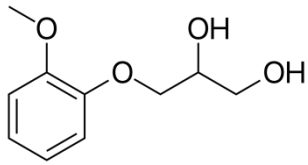
Its empirical formula is C12H19NO3 and its molecular weight is 225.284 g/mol.

Ambroxol belongs to a group of medications called mucolytics. Its chemical name is (1r,4r)-4-{[(2-amino-3,5-dibromophenyl)methyl]amino}cyclohexan-1-ol hydrochloride and its structure is:



Its empirical formula is $C_{13}H_{19}Br_2ClN_2O$ and its molecular weight is 414.56 g/mol.

Guaiphenesin is in a class of medications called expectorants. Its chemical name is 3-(2-methoxyphenoxy)propane-1,2-diol and its chemical structure is:



Its empirical formula is C10H14O4 and its molecular weight is 198.216 g/mol.

8. Pharmaceutical particulars

8.1 Incompatibilities

There are no known incompatibilities.

8.2 Shelf-life

24 months.

8.3 Packaging Information

Kofarest Syrup is available in bottle of 100ml.

8.4 Storage and handling instructions

Store below 25^{o}C. Protect from light.

9. Patient Counselling Information

9.1 Adverse Reactions

Refer part 4.8

9.2 Drug Interactions

Refer part 4.5

9.3 Dosage

Refer part 4.2

9.4 Storage

Refer part 8.4

9.5 Risk Factors

Refer part 4.4

9.6 Self-monitoring information

NA

9.7 Information on when to contact a health care provider or seek emergency help

Patient isadvised to be alert for the emergence or worsening of the adverse reactions and contact the prescribing physician.

9.8 Contraindications

Refer part 4.3

10. Manufactured by

CENTAUR PHARMACEUTICALS PVT. LTD. , Lab Daffodil and Goa Antibiotics

11. Details of permission or license number with date

158(188)/MFG/DFDA/2013/876 dated. 10.06.2013 for export to Nigeria.

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158(188)/MFG/DFDA/2012/27 dated. 02.04.2012 for export to Macau.

158(188)/MFG/DFDA/2011/4169 dated. 19.10.2011 for export to Mozambique.

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