Kofarest-DX Syrup

1. Composition

Dextromethorphan	10mg
Chlorpheniramine maleate (CPM)	2mg
Menthol	1.5mg

2. Dosage form and strength

Kofarest-DX Syrup is available in bottle of 100ml.

3. Clinical particulars

3.1 Therapeutic indication

Kofarest D X is indicated for Non-productive cough due to:

- Smoking
- Allergy
- Eosinophilia
- Bronchitis
- Tuberculosis and
- Whooping cough.

3.2 Posology and method of administration

Recommended oral dose for Kofarest DX Syrup is:

- Adults are 5-10 ml three times a day.
- children 6-12 years of age is 1-2 teaspoonful three times a day
- Children 2-6 years of age are ½-1 teaspoonful three times a day.

3.3 Contraindication

The use of Kofarest D X is contraindicated in patients with:

- hypersensitivity to any ingredient of the formulation
- Asthmatic attacks or severe cardiovascular disorders.

3.4 Special warnings and precautions for use

- Caution is needed in patients with a history of asthma and it should not be given during an acute attack.
- Care is also advisable in patients with bronchitis, emphysema, or in other conditions where chronic or persistent cough occurs**.**

3.5 Drug interactions

- Dextromethorphan is primarily metabolised by the cytochrome P450 isoenzyme CYP2D6 hence the possibility of interactions with inhibitors of this enzyme, including amiodarone, haloperidol, propafenone, quinidine,SSRIs, and thioridazine.
- CPM may interact with antihistamines applied to the skin(such as diphenhydramine cream, ointment, spray), antispasmodics (e.g., atropine, belladonna alkaloids), drugs for Parkinson's disease (e.g., anticholinergics such as benztropine, trihexyphenidyl), scopolamine, tricyclic antidepressants (e.g., amitriptyline).

3.6 Use in special population

- Pediatric: IAP Pediatric Drug Formulary, 2012 states 1.25 - 2 mg/kg/dose 4 times a day, and not per kg/day in 4 divided doses. As such there should be no problem in recommending appropriate doses of Kofarest DX, whenever necessary.
- Geriatric: Elderly population may be at greater risk for the side-effects.
- Liver impairment: Use with caution.
- Renal failure: Use with caution.
- Pregnancy and lactation: US Food and Drug Administration (FDA) has specified Chlorphenamine maleate as a pregnancy category B drug which indicates that animal and human studies have failed to demonstrate a risk to the fetus in any trimester. Doctor consultation recommended.

3.7 Effects on ability to drive and use machine

Kofarest D X may cause drowsiness. Therefore, it is advisable not to operate machinery or drive when on this medication.

3.8 Undesirable effects

Adverse events associated with the use of Kofarest D X are rare. It may occasionally cause nausea, vomiting or gastrointestinal disturbance. Other possible adverse reactions include rash or itching, drowsiness, excitability, nervousness, restlessness, sleeplessness, dizziness and palpitations.

3.9 Overdose

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

4. Pharmacological properties

4.1 Mechanism of action

Dextromethorphan is an opioid-like drug that binds to and acts as antagonist to the NMDA glutamatergic receptor, it is an agonist to the opioid sigma 1 and sigma 2 receptors, it is also an alpha3/beta4 nicotinic receptor antagonist and targets the serotonin reuptake pump. Dextromethorphan is rapidly absorbed from the gastrointestinal tract, where it enters the bloodstream and crosses the blood-brain barrier. The first-pass through the hepatic portal vein results in some of the drug being metabolized into an active metabolite of dextromethorphan, dextrorphan, the 3-hydroxy derivative of dextromethorphan.

In allergic reactions an allergen interacts with and cross-links surface IgE antibodies on mast cells and basophils. Once the mast cell-antibody-antigen complex is formed, a complex series of events occurs that eventually leads to cell-degranulation and the release of histamine (and other chemical mediators) from the mast cell or basophil. Once released, histamine can react with local or widespread tissues through histamine receptors. Histamine, acting on H1-receptors, produces pruritis, vasodilatation, hypotension, flushing, headache, tachycardia, and bronchoconstriction. Histamine also increases vascular permeability and potentiates pain. Chlorpheniramine maleate binds to the histamine H1 receptor. This block the action of endogenous histamine, which subsequently leads to temporary relief of the negative symptoms brought on by histamine.

Menthol has a cooling and soothing effect.

4.2 Pharmacodynamic properties

Dextromethorphan suppresses the cough reflex by a direct action on the cough center in the medulla of the brain. Dextromethorphan shows high affinity binding to several regions of the brain, including the medullary cough center. This compound is an NMDA receptor antagonist and acts as a non-competitive channel blocker. It is one of the widely used antitussives, and is also used to study the involvement of glutamate receptors in neurotoxicity.

Chlorpheniramine maleate is a histamine H1 antagonist of the alkylamine class. It competes with histamine for the normal H1-receptor sites on effector cells of the gastrointestinal tract, blood vessels and respiratory tract. It provides effective, temporary relief of sneezing, watery and itchy eyes, and runny nose due to hay fever and other upper respiratory allergies.

4.3 Pharmacokinetic properties

Dextromethorphan is rapidly absorbed from the gastrointestinal tract. It is metabolised in the liver and excreted in the urine as unchanged dextromethorphan and demethylated metabolites including dextrorphan, which has some cough suppressant activity.

Chlorphenamine maleate is absorbed relatively slowly from the gastrointestinal tract, peak plasma concentrations occurring about 2.5 to 6 hours after oral doses. Bioavailability is low, values of 25 to 50% having been reported. Chlorphenamine appears to undergo considerable first-pass metabolism. About 70% of chlorphenamine in the circulation is bound to plasma proteins. There is wide inter individual variation in the pharmacokinetics of chlorphenamine; values ranging from 2 to 43 hours have been reported for the half-life. Chlorphenamine is widely distributed in the body, and enters the CNS. Chlorphenamine maleate is extensively metabolised. Metabolites include desmethyl- and didesmethylchlorphenamine. Unchanged drug and metabolites are excreted primarily in the urine; excretion is dependent on urinary pH and flow rate. Only trace amounts have been found in the faeces. Duration of action of 4 to 6 hours has been reported; this is shorter than may be predicted from pharmacokinetic parameters. More rapid and extensive absorption, faster clearance, and a shorter half-life have been reported in children.

5. Nonclinical properties

5.1 Animal Toxicology or Pharmacology

Not required.

6. Description

Already mentioned and covered in the above points.

7. Pharmaceutical particulars

7.1 Incompatibilities

There are no known incompatibilities.

7.2 Shelf-life

24 months.

7.3 Storage and handling instructions

Store in cool and dry place.

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