Kofarest-DX Syrup

Composition:

Each 5ml contains:

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

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.

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 H_1-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.

Other 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 H_1-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.

Indication:

Kofarest D X is indicated for, Non-productive cough due to smoking, allergy, eosinophilia, bronchitis, tuberculosis and whooping cough.

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.

Drug Interaction:

- 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).

Adverse 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.

Warnings and Precautions:

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

Use in special population:

1. **Pediatric:** IAP Pediatric Drug Formularly, 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.
2. **Geriatric:** Elderly population may be at greater risk for the side-effects.
3. **Liver impairment:** Use with caution.
4. **Renal failure:** Use with caution.
5. **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.

Dosage:

The usual recommended dose of Kofarest D X in

- 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.

Presentation:

Kofarest D X is available in a bottle of 60 ml.

Storage and handling:

Store below 30 ^{o}C in a dark and dry place.