Kofarest-LD Syrup

1. **Generic Name:** Levodropropizine, Chlorpheniramine Maleate (CPM).

2. **Qualitative and Quantitative composition**

Each 5ml contains:

Levodropropizine IP	30 mg
Chlorpheniramine Maleate IP	2 mg

3. **Dosage form and strength**

Kofarest LD is available in the bottle of 100 ml.

4. **Clinical particulars**

4.1 Therapeutic indication

Symptomatic treatment of dry cough of various origins.

4.2 Posology and method of administration

The recommended oral dose of Kofarest LD for adults is 5-10 ml TID for 5 days or as directed by the physician.

4.3 Contraindication

Kofarest LD is contraindicated in known or suspected cases of hypersensitivity, during the period of pregnancy and lactation, in severe hepatic disorders, and in patients with bronchorrhea and reduced mucociliary function (such as Kartagener syndrome, ciliary dyskinesia).

4.4 Special warnings and precautions for use

In case of severe renal failure (creatinine clearance <35 ml/min), it should be used cautiously with benefit/risk ratio taken into consideration. Antitussive agents are for symptomatic treatment and only should be used accordingly until treatment of underlying pathology is ensured and/or the triggering causes are identified. Therefore, long term treatment with Kofarest LD should be avoided. Consult a doctor if no significant improvement achieved after a short course of treatment.

Based on the observation that pharmacokinetic profile of levodropropizine has not been altered remarkably in elderly patients, dose adjustment or modification of the intervals between the doses may not be necessary. However, since elderly patients have been known to vary in their sensitivity reactions toward many drugs, Levodropropizine administration in this age group should require special consideration.

4.5 Drug interactions

Although in clinical trials no drug interaction with benzodiazepines were observed, careful administration of the drug is necessary especially in sensitive patients using sedative agents.

Animal pharmacology studies have demonstrated that levodropropizine does not potentiate the pharmacological effect of substances acting on the central nervous system (e.g. benzodiazepines, alcohol, phenytoin, and imipramine). In animals, levodropropizine did not modify the activity of oral anticoagulants, such as warfarin, and did not interfere with the hypoglycemic effect of insulin.

In human pharmacology studies, the combination with benzodiazepines does not modify the EEG pattern. Caution is necessary in concomitant use of sedative drugs particularly in sensitive subjects.

Clinical studies did not show any interaction with drugs used for the treatment of bronchopulmonary pathologies, such as beta-2-agonists, methylxanthine and derivatives, corticosteroids, antibiotics, mucoregulators, and antihistamines.

4.6 Use in special population

- Pediatric: Contraindicated in children below 2 years of age
- Geriatric: No dosage or interval modification needed in elderly people
- Liver impairment: Use with caution
- Renal failure: Use cautiously in patients with severe renal failure (creatinine clearance < 35ml/min).
- Pregnancy and lactation: Levodropropizine is contraindicated in pregnant females and during lactation.

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 LD is known.

4.8 Undesirable effects

Adverse reaction established to be drug related are listed below: Frequency is defined as: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1.000 to < 1/100), rare (≥1/10.000 to <1/10.000); not known (cannot be estimated from the available data).

Immune system disorders

Very rare: Hypersensitivity reactions.

Psychiatric disorders
Very rare: Nervousness, somnolence, depersonalization.

Immune system disorders
Very rare: Tiredness-asthenia, lethargy, drowsiness, headache, vertigo, tremor, and paresthesia. An individual case of tonic-clonic convulsions and petit mal episode has been reported.

Eye diseases
Individual cases of mydriasis and of loss of the bilateral visual faculty have been reported. In both cases, the reactions resolved following the discontinuation of the drug.

Cardiac diseases
Very rare: Palpitation, tachycardia. An individual case of atrial bigeminy has been reported.

Vascular disorders
Very rare: Hypotension

Respiratory, thoracic and mediastinal disorders
Very rare: Dyspnea, cough, edema of the respiratory tract.

Gastrointestinal disorders
Very rare: Nausea, vomiting, heartburn and gastralgia, dyspepsia, and diarrhea. Two individual cases of glossitis and aphthous stomatitis have been reported. An individual case of cholestatic hepatitis and another case of hypoglycemic coma in an elderly patient receiving concomitant oral hypoglycemic agents have been observed.

Skin and subcutaneous tissue disorders
Very rare: Allergic skin eruption, urticaria, erythema, exanthema, itching, and angioedema. An individual case of epidermolysis with fatal outcome has been reported.

Musculoskeletal and connective tissue disorders
Very rare: Asthenia and weakness of lower extremities.

General disorders and administration site disorder
Very rare: Allergic and anaphylactoid reactions. General malaise. Individual cases of generalized edema, syncope, and asthenia have been rarely reported. An individual case of sleepiness, hypotonia and vomiting in a newborn has been reported after the administration of levodropropizine in the lactating mother. In

this case, symptoms, which appeared after breastfeeding, spontaneously resolved after discontinuing breastfeeding.

4.9 Overdose

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

5. Pharmacological properties

5.1 Mechanism of action

Levodropropizine is a peripherally acting antitussive agent. Levodropropizine inhibit the cough reflex by acting on the peripheral receptors and their afferent conductors. Levodropropizine inhibits the C-fibers of the vagus nerves and modulate the sensory neuropeptides production in the respiratory tract, involved in the cough reflex. Levodropropizine has a dose-dependent and short-term local anaesthetic activity. It also has a mild analgesic and an antihistaminic action.

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 blocks the action of endogenous histamine, which subsequently leads to temporary relief of the negative symptoms brought on by histamine.

5.2 Pharmacodynamic properties

Levodropropizine is a peripherally acting antitussive working at tracheobronchial level. The peripheral action has been demonstrated in animal studies. Its mechanism provides this drug antitussive properties against cough associated to different lung pathologies, but without relevant central side effects. Levodropropizine inhibits bronchospasms induced by histamine, serotonin and bradykinin. Levodropropizine exerts its antitussive effect through an inhibitory action at the level of the airway sensory nerves involving modulation of sensitive C-fibers and release of neuropeptides.

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.

5.3 Pharmacokinetic properties

Levodropropizine

Absorption: Bioavailability of levodropropizine was found to be greater than 75% after oral administration. Plasma protein binding rate was lower (11-14%).

Distribution: In human, oral levodropropizine was rapidly absorbed and distributed throughout the body.

Biotransformation: There is no data about the specific site of metabolism of levodropropizine either in the liver or in other sites.

Elimination: Plasma elimination half-life of levodropropizine is approximately 1-2 hours. Its excretion is mainly in the urine. Elimination of the active substance is either in the form of both unchanged and conjugated or free levodropropizine or in conjugated p-hydroxy-levodropropizine metabolites. Elimination of the active substance and its metabolites in 48 hours approximates to 35% of the administered dose. Results of the repeat dose studies have demonstrated that 8 days of treatment (3 times a day) did not alter the elimination characteristics of the drug and therefore accumulation or metabolic auto-induction were unlikely.

Chlorpheniramine maleate

Absorption: 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.

Distribution: Chlorphenamine is widely distributed in the body and enters the CNS.

Biotransformation: 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 maleate is extensively metabolised. Metabolites include desmethyl- and didesmethylchlorphenamine.

Elimination: 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.

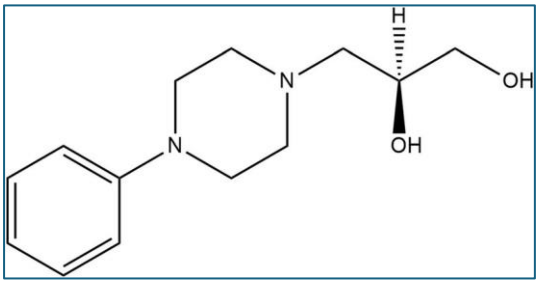
6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Not required.

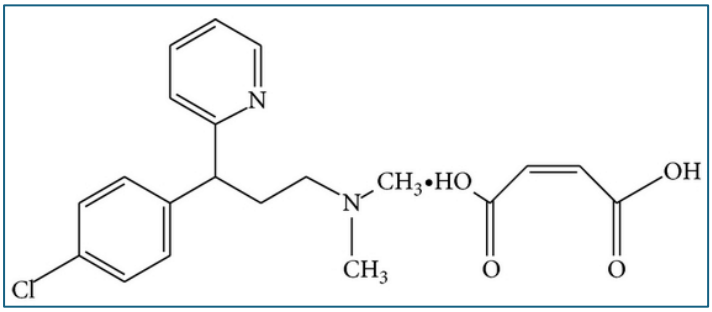
7. Description

Levodropropizine belongs to class of medicines called antitussives. Its chemical name is (2S)-3-(4-Phenylpiperazin-1-yl)propane-1,2-diol. The structure is depicted below:



Its molecular formula is C13H20N2O2 and its molecular weight is 236.315 g/mol

Chlorpheniramine maleate is in a class of medications called antihistamines. Its chemical name is (2Z)-but-2-enedioic acid; [3-(4-chlorophenyl)-3-(pyridin-2-yl)propyl]dimethylamine and its structural formula is :



Its molecular formula is C16H19ClN2.C4H4O4 or C20H23ClN2O4 and its molecular weight is 390.9 g/mol.

8. Pharmaceutical particulars

8.1 Incompatibilities

There are no known incompatibilities.

8.2 Shelf-life

24 Months

8.3 Packaging Information

Kofarest LD is available in bottle of 100 ml.

8.4 Storage and handling instructions

Store in cool and dry place.

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 is advised 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

SGS Formulation Pvt Ltd.

11. Details of permission or licence number with date

TN00004461

12. Date of revision

May 2025