# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF MEDICINAL PRODUCT
DROPOLEV 60 mg/ml ORAL DROPS 30 ml

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 1 ml solution contains:

**Active substance:**

| | |
|---|---|
| Levodropropizine | 60 mg |

**Excipients:**

| | |
|---|---|
| Sucrose | 133.33 mg |
| Methyl paraben sodium | 1.30 mg |
| Sodium Saccharin | 3.33 mg |
| FD&C yellow # 6 | 0.10 mg |

For a full list of excipients, see Section 6.1.

## 3. PHARMACEUTICAL FORM
Drops

Yellow to orange and clear solution with aromatic odor

## 4. CLINICAL PARTICULARS
### 4.1. Therapeutic indications
It is indicated in symptomatic treatment of dry cough (nonproductive cough) due to various causes.

### 4.2. Posology and method of administration
**Posology/Frequency and duration of administration:**

*Adults:*
It is administered 20 drops (60 mg levodropropizine; 1 drop 0.05 ml) 3 times/day with at least 6-hour intervals between doses

*Children:*
For children older than 2 years of age, it is used 3 times daily with at least 6-hour-intervals and as follows:

| Body weight (kg) | Number of drops per use | Body weight (kg) | Number of drops per use |
|---|---|---|---|
| 7-10 | 3 | 29-31 | 10 |
| 11-13 | 4 | 32-34 | 11 |
| 14-16 | 5 | 35-37 | 12 |
| 17-19 | 6 | 38-40 | 13 |
| 20-22 | 7 | 41-43 | 14 |
| 23-25 | 8 | 44-46 | 15 |
| 26-28 | 9 | >46 | 20 |

The drug is taken until the cough disappears or as indicated by the doctor and maximum treatment duration of 7 days should not be exceeded. If the symptoms do not disappear within this period, medication should be temporarily discontinued and a doctor should be consulted

**Method of Administration:**
For oral use only.
It is recommended to take shorty before or after the meals, although no effect on absorption have been reported when taken with food.
Drops should preferably be taken with half a glass of water.

**Additional information on special populations:**
**Renal/Hepatic Failure:** In cases of severe kidney failure (creatinine clearance <35 ml/min), should be used cautiously with benefit risk ratio taken into consideration.

**Pediatric population:** DROPOLEV ORAL DROPS should be used in pediatric patients as indicated in the posology section. It should not be used in children under 2 years of age.

**Geriatric population:** DROPOLEV ORAL DROPS dosage in elderly patients should be carefully adjusted.

**4.3. Contraindications**
It 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 cases of severe kidney failure (creatinine clearance <35 ml/min), it should be used cautiously with benefit/risk ratio taken into consideration. Antitussive agents are for symptomatic treatment only and should be applied accordingly until treatment of underlying pathology is ensured and/or the triggering causes are identified. Therefore, long-term treatment with DROPOLEV ORAL DROPS 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.

Since 20 drops contain 0.35 g sucrose, patients with rare hereditary fructose intolerance, and glucose-galactose malabsorption, or sucrase-isomaltase insufficiency should avoid using the drug.

DROPOLEV ORAL DROPS contains methyl paraben sodium, which may cause allergic reactions (probably delayed).

This medicinal product contain less than 1 mmol (23 mg) sodium per ml; i.e., it essentially “does not contain sodium”.

DROPOLEV ORAL DROPS contains FD&C yellow # 6, which may cause allergic reactions.

**4.5. Interactions with other medicinal products and other forms of 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. See section 4.4)

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. Pregnancy and lactation**
**General recommendation**
Pregnancy category: D

**Women with childbearing potential/Birth control (Contraception)**
Women with childbearing potential either should avoid using the drug, or should use effective contraceptive methods.

**Pregnancy**
In animal toxicology studies, a mild delay in the weight gain and in growth has been observed with 24 mg/kg dose. Levodropropizine is able to cross the placental barrier in rats, therefore is contraindicated in women, intent to get pregnant or already pregnant.
Levodropropizine did not have any harmful pharmacological effect in pregnancy and/or on fetus/neonates.

**Lactation**
In studies in rats, levodropropizine was found in breast milk after 8 hours of administration.
Levodropropizine crosses breast milk. Therefore should not be used during lactation.

**Reproduction/ Fertility**
In addition to peri- and post-natal studies, fertility studies as well did not show any specific toxic effect.

**4.7. Effects on ability to drive and use of machines**
Although no studies have been performed on the ability to drive and use of machines, it may cause sleepiness (see section 4.8) therefore should be used very cautiously when driving or using machine. Patients should necessarily be informed about this possible effect.

**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 <1/1.000); very rare (<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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Turkish Pharmacovigilance Center (TÜFAM). (www.titck.gov.tr; e-mail: tufam@titck.gov.tr; tel.: 800 314 00 08; fax: 0 312 218 35 99).

**4.9. Overdose**

No serious side effect was observed following the administration of a single dose of levodropropizine up to 240 mg or 120 mg 3 times a day for 8 days.

No incident of levodropropizine overdose has been reported. However, in case of overdose, a mild, temporary tachycardia might be observed. One isolated case of levodropropizine overdose have been reported in which a 3-year-old child were given treatment with a dosage of 360 mg/day. The patient experienced abdominal pain and nausea, which were not severe and resolved spontaneously without any complication. In case of overdose, following precautions should be administered to avoid intoxication: gastric lavage, active carbon, and initiation of parenteral liquid treatment. No specific antidote is available.

**5. PHARMACOLOGICAL PROPERTIES**

**5.1. Pharmacodynamic properties**

Pharmacotherapeutic group: Other Cough Suppressants

ATC Code: R05DB27

Antitussive activity of levodropropizine is tracheobronchial and peripheral. It shows an inhibitory effect on C-fibers and inhibits the release of neuropeptides.

The antitussive activity of Levodropropizine after oral administration in animals was similar to or greater than the effects of dropropizine and cloperastine on cough induced by peripheral stimulation, such as chemical substances, mechanical stimulation of the trachea and electrical stimulation of the vagal afferens. Activity on cough induced by central stimulation, as in tracheal electrical stimulation in guinea pigs, was 10 times lower than that of codeine. However, the potency ratio of these two drugs was 0.5 to 2 in peripheral stimulation tests with citric acid, ammonium hydrate, and sulfuric acid.

Levodropropizine, when given intracerebroventricularly in animals, was not active. This suggests that the antitussive activity of the compound was due to a peripheral mechanism, rather than central nervous system. Comparison of the antitussive efficacy of Levodropropizine and codeine in experimentally induced cough in guinea pigs after oral and aerosol administration have confirmed the peripheral site of action of Levodropropizine. In fact, Levodropropizine has comparable activity to or more potent than codeine given as an aerosol, but twice less potent than codeine given orally.

As it is the case with mechanism of action, the antitussive activity of Levodropropizine is mediated through its inhibitory action on C-fibres. In particular, Levodropropizine has been shown to inhibit "*in vitro*" release of sensory neuropeptides from C-fibres. In anesthetized cats, Levodropropizine has markedly reduced the activation of C-fibres and abolished associated reflexes.

Levodropropizine has significantly lower activity than dropropizine on oxotremorine-induced tremors and pentamethylenetetrazole-induced convulsions and in modifying the spontaneous motility in mice.

Levodropropizine did not replace naloxone at opioid receptors in mice brain; did not alter the morphine-induced withdrawal syndrome; and discontinuation of it was not followed by the onset of addictive behaviors.

Levodropropizine did not cause depression of respiratory function in animals or any significant cardiovascular effects, nor does it induce constipation effects.

Levodropropizine exerted its activity on the bronchopulmonary system by inhibiting bronchospasm, induced by histamine, serotonin and bradykinin. It did not inhibit acetylcholine-induced bronchospasm that demonstrates that it has no anticholinergic effects.
In animals, $ED_{50}$ of antibronchospastic activity is comparable to the corresponding value for antitussive activity.

In healthy volunteers, 60 mg dose has reduced the cough, induced by citric acid aerosol, for at least 6 hours.

The clinical efficacy of Levodropropizine in reducing cough of various etiologies, such as cough due to bronchopulmonary carcinoma, infections of the upper and lower airways, and pertussis has been established by many experimental evidences. The antitussive activity is generally comparable to that of centrally active drugs. Levodropropizine has a better tolerability profile mainly for central sedative effects.

At therapeutic doses, Levodropropizine did not affect EEG patterns and psychomotor functions. In healthy volunteers, Levodropropizine up to 240 mg did not alter cardiovascular parameters.

The drug did not cause respiratory depression, or interfere with mucociliary clearance in humans. In particular, a recent study has demonstrated that Levodropropizine did not produce depression on the central regulation of respiration in patients with chronic respiratory failure, in both spontaneous breathing and hypercapnic ventilation.

**5.2. Pharmacokinetic properties**

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 altered the elimination characteristics of the drug and therefore accumulation or metabolic auto-induction were unlikely.

**5.3. Preclinical safety data**
Acute oral toxicity is 886.5 mg/kg, 1287mg/kg and 2492 mg/kg, respectively in rats, mice and guinea pigs. In guinea pigs, the therapeutic index calculated as the ratio of $LD_{50}/ED_{50}$after oral administration was 16 to 53, depending on the cough induction model. Toxicity tests for repeated oral administrations have shown that the daily dose without toxic effect corresponds to 24 mg/kg.

## 6. PHARMACEUTICAL PARTICULARS

**6.1. List of excipients**
Methyl paraben sodium
Propylene glycol
Sucrose
Citric acid monohydrate
Mint flavor
Aniseed flavor
Flavoring agent
FD&C yellow # 6
Sodium Saccharine
Deionized water

**6.2. Incompatibilities**
Not reported.

**6.3. Shelf life**
24 months

**6.4. Special precautions for storage**
Store at room temperature below 25°C away from light.

**6.5. Nature and contents of container**
DROPOLEV ORAL DROPS is marketed in non-parenteral amber colored (Type III) glass bottle, closed with a pilfer-proof high density polyethylene (HDPE) cap with low density polyethylene (LDPE) dropper.

Each cardboard box contains one bottle.

**6.6. Special precautions for disposal and other handling**
Any unused product or waste material should be disposed of in accordance with “Directive on Control of Medical Waste” and “Directive on the Control of Package and Packaging Waste.”

**7. MARKETING AUTHORIZATION HOLDER**

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**8. MARKETING AUTHORIZATION NUMBER(S)**

2014/321

**9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION**

Date of the first authorization: 17.04.2014
Date of the renewal of the authorization:

**10. DATE OF REVISION OF THE TEXT**

17/04/2014