

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

PULMOREST® 30mg/5ml syrup

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Substance:

For 1 ml syrup:	
Levodropropizine	6.0 mg

Excipients:

Sucrose	300.0 mg
Methyl parahydroxybenzoate (E218)	1.3 mg
Propyl parahydroxybenzoate (E216)	0.2 mg
Sodium Hydroxide	3.6 mg

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Syrup

Colorless or pale yellow clear liquid.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

It is indicated for the symptomatic treatment of non-productive cough caused by several reasons.

4.2. Posology and method of administration

Posology/administration frequency and duration:

Adults:

10 ml (60 mg) syrup (until the 10 ml line on the scale) is administered 3 times per day with at least 6-hour intervals.

Children:

It is administered to the children older than 2 years.

It is administered as 3-6 mg per kilogram per day depending on the severity of the symptoms with at least 6-hour interval by portioning into 3 equal dose.

It is administered;

For patients weighing between 10-20 kg, 3 ml (until line of 3 ml on scale) 3 times per day

For patients weighing between 20-30 kg, 5 ml (until line of 5 ml on scale) 3 times per day

For patients weighing over 30 kg, 10 ml (until line of 10 ml on scale) 3 times per day

The medicinal product must be administered according to the medical advice or until the cough disappears providing that it does not last longer than 7-day treatment period. If the symptoms do not disappear in this period, the administration of the medicinal product should be interrupted and a medical advice should be sought.

Method of Administration:

It is only indicated for oral administration.

Even though there is no information regarding the effect of the administration of this medicinal product with food on absorption, it is suggested to administer the medicine some time before or after meal. Can be administered using a measuring device.

Additional information related to special populations

Patients with renal/liver impairment: In severe renal impairment cases, it must be administered by considering the benefit-risk rate.

Pediatric Population: PULMOREST® should be administered as indicated in the dosage section for pediatric patients. Its use is contraindicated in children under 2 years of age. Use in children under 6 years is not recommended.

Geriatric Population: Studies indicate that the pharmacokinetic profile of levodropropizin does not change significantly in elderly patients, suggesting that no adjustments in dosage or administration frequency are necessary. However, due to variability in sensitivity to various medications in elderly patients, PULMOREST® should be administered with caution in this population.

4.3. Contraindications

It is contraindicated in cases of known or suspected hypersensitivity to the drug, during pregnancy and lactation, in children under 2 years of age, in people with severe hepatic insufficiency, in cases of bronchorrhea and reduced mucociliary clearance mechanism (such as Kartagener syndrome or ciliary dyskinesia).

4.4. Special warnings and precautions for use

In cases of severe renal failure; (creatinine clearance < 35 ml/min); should be used with caution considering the benefit-risk ratio.

Cough medicines provide symptomatic treatment and should be used until the underlying pathology is treated and/or the triggering cause is determined. If no significant result is obtained after a short-term treatment (2 weeks), a doctor should be consulted or the treatment should be discontinued.

Levodropropizin is contraindicated for use under the age of 2. It is not recommended for use under the age of 6.

Since 10 ml syrup contains 3 g sucrose, patients with rare hereditary fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency problems should not use this medicine.

The medicine contains methyl parahydroxybenzoate and propyl parahydroxybenzoate, which have been reported to cause urticaria. Parahydroxybenzoate can generally cause delayed reactions such as contact dermatitis and rarely immediate reactions such as urticaria and bronchospasm.

4.5. Interaction with other medicinal products and other forms of interaction

Although no interaction with benzodiazepines has been observed during clinical studies, caution should be exercised when used in sensitive patients, especially those receiving sedative drugs. Animal pharmacology studies have shown that levodropropizine does not potentiate the pharmacological effects of substances acting on the central nervous system (e.g., benzodiazepines, alcohol, phenytoin, imipramine). Levodropropizine does not alter the effects of oral anticoagulants such as warfarin in animals, and also does not affect the hypoglycemic effect of insulin. In human pharmacology studies, concomitant use with benzodiazepines did not alter the EEG pattern. Caution should be exercised when used together with sedative drugs, especially in sensitive cases. Clinical studies have not shown any interaction with drugs used in the treatment of bronchopulmonary pathologies, such as beta-2 agonists, methylxanthines and their derivatives, corticosteroids, antibiotics, mucoregulators and antihistamines.

Additional information related to special populations

No interactions have been reported.

Pediatric population:

There are no interaction studies on the pediatric population.

4.6. Pregnancy and Lactation

General Recommendation

Its pregnancy category is D.

Women with childbearing potential/Contraception

Women with childbearing potential should not use this medicinal product, and should apply an effective birth control method.

Pregnancy period

Levodropropizine crosses the placental barrier. It has been proven to have harmful effects on the fetus in humans, therefore it should not be used in pregnant women. In animal toxicology studies, it was observed that a dose of 24 mg/kg caused a slight delay in body weight gain and growth. Since Levodropropizine can cross the rat placental barrier, it is contraindicated in pregnant women and those considering pregnancy, as its safety has not been proven (See Section 4.3).

Lactation period

In rat experiments, the drug was detected in breast milk within 8 hours following administration. Levodropropizin passes into breast milk. Therefore, it should not be administered in breastfeeding mothers.

Fertility

No specific toxic effect has been observed in fertility studies carried out in addition to perinatal and post-natal studies.

4.7. Effects on ability to drive and use machines

However, there is no study carried out regarding its effects on ability to drive and use machines, patients should be careful while driving or using machines since it may cause drowsiness (See Section “4.8 Undesirable effects”).

4.8. Undesirable effects

The undesirable effects are evaluated according to the frequencies stated below:

Very common ($\geq 1/10$); Common ($\geq 1/100$ and $< 1/10$); Uncommon ($\geq 1/1,000$ and $< 1/100$); Rare ($\geq 1/10,000$ and $< 1/1,000$); Very rare ($\geq 1/10,000$), unknown (unpredictable from the available data).

Immune system disorders

Very rare: Hypersensitivity disorder.

Psychiatric disorders

Very rare: Anxiety, drowsiness, depersonalization

Nervous system disorders

Very rare: Fatigue-asthenia, malaise, hypokinesia, head ache, vertigo, tremor, paresthesia.

Cardiovascular disorders

Very rare: Palpitations, tachycardia, arrhythmias.

Vascular disorders

Very rare: hypertension

Respiratory, thoracic and mediastinal disorders

Very rare: Dyspnea, cough, edema in respiratory tracts.

Gastrointestinal disorders

Very rare: Nausea, vomiting, heartburn and stomach ache, dyspepsia, diarrhea. Glossitis and aphthous were reported in two cases.

Skin and subcutaneous tissue disorders

Very rare: Allergic skin rashes, urticaria, erythema, exanthema, pruritus, angioedema.

Reporting of suspicious adverse events

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 to Turkish Pharmacovigilance Center (TÜFAM) at: www.titck.gov.tr; e-mail: tufam@titck.gov.tr; phone: 0 800 314 00 08; fax: 0 312 218 35 99.

4.9. Overdose/Treatment

No serious adverse effects have been observed after a single dose of up to 240 mg or after administering 120 mg three times daily for 8 days. In the event of a possible overdose, mild and transient tachycardia may occur. It is known that an overdose case was reported in a 3-year-old child treated with a daily dose of 360 mg of levodropropizin. The mild abdominal pain and nausea observed in the patient resolved without any complications. In cases of overdose confirmed by clinical findings, symptomatic treatment should be initiated immediately, and traditional first aid measures (gastric lavage, activated charcoal, parenteral fluids, etc.) should be applied if necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic class: Other cough suppressant drugs

ATC code: R05DB27

Levodropropizin exhibits its antitussive effect peripherally at the tracheobronchial level. It demonstrates an inhibitory effect on C fibers and inhibits the release of neuropeptides. Levodropropizin is a stereospecific molecule produced and chemically corresponding to S(-)-3-(4-phenylpiperazin-1-yl)-propan-1,2-diol. It primarily serves as a peripheral tracheobronchial antitussive agent, along with antiallergic and antibronchospastic effects. It also shows local anesthetic effects in animal studies.

In animals, following oral administration, the antitussive activity of Levodropropizin has been found to be equal to or greater than that of its chemical counterparts, Dropropizin and Cloperastin, and is influenced by peripheral stimulation induced by mechanical irritations of the trachea and electrical stimulation of vagal afferents. In guinea pigs, the effects of Levodropropizin on cough induced by central stimuli, such as electrical stimulation of the trachea, were found to be approximately 10 times lower than that of codeine; in peripheral stimulation tests, such as citric acid, ammonium hydroxide, and sulfuric acid tests, the potency ratio between the two drugs ranged from 0.5 to 2.

Levodropropizin is inactive when administered intracerebroventricularly in animals, indicating that its antitussive effect operates through a peripheral mechanism and does not affect the central nervous system. Additionally, comparisons of the effects of Levodropropizin administered as an aerosol and orally with codeine in preventing experimentally induced cough in guinea pigs confirm the peripheral effects of Levodropropizin. In fact, Levodropropizin shows equal or greater activity than codeine when administered as an aerosol. However, when given orally, its effect is about half that of codeine.

Levodropropizin exerts its antitussive activity through its inhibitory effect on C fibers, particularly inhibiting the release of sensory neuropeptides from C fibers "in vitro." It significantly reduces the activation of C fibers in anesthetized cats, thereby eliminating the related reflexes.

The effect of Levodropropizin on tremors induced by oxotremorine in mice, as well as its effect on convulsions induced by pentylene tetrazole and changes in spontaneous movement, is significantly lower compared to Dropropizin. Levodropropizin does not displace naloxone from opioid receptors in the brains of rats and does not alleviate morphine-induced withdrawal syndrome; the cessation of the drug's administration is not associated with the onset of addictive behaviors.

In animals, Levodropropizin does not cause respiratory function depression, significant cardiovascular effects, or induce constipation. It acts by inhibiting bronchospasm induced by histamine, serotonin, and bradykinin in the broncho-pulmonary system. Due to the absence of anticholinergic effects, it does not inhibit bronchospasm induced by acetylcholine. In animals, the ED₅₀ value for antibronchospastic activity is similar to that of its antitussive activity.

In healthy volunteers, 60 mg of levodropropizin reduces cough induced by citric acid aerosol for at least 6 hours. Numerous experimental evidence demonstrates the clinical efficacy of

Levodropropizin in reducing cough associated with various etiologies, such as bronchopulmonary carcinoma, cough due to upper and lower respiratory tract infections, and whooping cough. Compared to drugs that affect the central nervous system, Levodropropizin generally has a better tolerability profile, particularly concerning central sedative effects, while its antitussive effects are usually comparable.

In humans, when administered at therapeutic doses, Levodropropizin does not affect EEG patterns or psychomotor abilities. No significant changes in cardiovascular parameters have been observed in healthy volunteers receiving up to 240 mg of Levodropropizin.

Levodropropizin does not suppress respiratory functions or mucociliary clearance in humans. Recent studies have demonstrated that Levodropropizin does not exert suppressive effects on the central respiratory regulation system during spontaneous breathing and hypercapnic ventilation in patients with chronic respiratory failure.

5.2. Pharmacokinetic properties

General properties

Absorption:

Bioavailability has been found as higher than 75% after oral administration. The binding with plasma proteins is low (11-14%).

Distribution:

Levodropropizin is rapidly absorbed and distributed quickly in the body after oral administration in human.

Biotransformation:

There is no data proving that levodropropizin is significantly metabolized in liver or any other part of the body.

Elimination:

Plasma elimination half-life of Levodropropizin is approximately 1-2 hours. The medicinal product is mainly secreted in urines. The secretion of the active matter is both as unchanged and as conjugated levodropropizin or free levodropropizin and conjugated p-hydroxyl-levodropropizin metabolites. The urinary secretion of this matter and its metabolites in 48 hours is equal to approximately 35% of the administered dose. Studies on repeated administration show that 8-day treatment with 3 dose per day does not change the elimination properties of the medicine and therefore, the phenomena of accumulation and self-induction is excluded.

5.3. Preclinical safety data

Oral acute toxicity is 886.5 mg/kg, 1287 mg/kg, 2492 mg/kg in rats, mice and guinea pigs, respectively. The therapeutic index in guinea pigs was calculated as LD₅₀/ED₅₀ ratio, is between 16-53 depending on the applied cough indication after oral administration. Toxicity tests following the repeated oral administrations have shown that the daily dos without any toxic effect is 24 mg/kg/day.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

- Sucrose

- Methyl parahydroxybenzoate (E218)
- Propyl parahydroxybenzoate (E216)
- Sodium hydroxide
- Citric acid monohydrate
- Cherry aroma
- Deionized water

6.2. Incompatibilities

Not reported.

6.3. Shelf Life

24 months.

6.4. Special precautions for storage

Store below 30°C and protect from light.

6.5. Nature and Contents of Container

It is presented in honey colored bottle containing 150 and 200 ml, with a measuring spoon for 10 ml and with its Package Insert in a box.

6.6. Special precautions for disposal from Human Medicinal Product and other handling

Products which are not used or waste materials should be disposed in accordance with “Medical Waste Control Regulations” and “Packaging and Packaging Waste Control Regulations” if applicable.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

228/78

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 31.12.2010

Date of latest renewal: -

10. DATE OF REVISION OF THE TEXT

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