

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

PULMOREST FORT 60mg/5ml syrup

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Substance:

For 1 mL syrup:

Levodropropizine	12 mg/mL
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Excipients:

Sucrose	300.0 mg/mL
Methyl parahydroxybenzoate (E218)	1.3 mg/mL
Propyl parahydroxybenzoate (E216)	0.2 mg/mL

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:

5 ml (60 mg) syrup (until the 5 ml line on the scale) is administered 3 times per day with at least 6-hour intervals.

Children:

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;

2,5 ml of syrup up to 3 times daily for children between 20 to 30 kg

5 ml of syrup up to 3 times daily for children over 30 kg.

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. The medical product should be used by pipette.

Additional information related to special populations

Patients with renal/liver impairment: In severe renal impairment cases (creatinine clearance <35 ml/min), it must be administered by considering the benefit-risk rate.

Pediatric population: PULMOREST FORT should be administered to pediatric patient as stated in the “**Posology/Administration frequency and duration**” section. PULMOREST FORT is contraindicated in less than two years old children. It is not recommended for the children younger than six years old. For pediatric patients weighing between 10-20 kg, 1,5 ml PULMOREST® FORT should be taken 3 times per day

Geriatric population: Dosage of PULMOREST FORT® should be determined carefully for the geriatric patients.

4.3. Contraindications

It is contraindicated;

- In known or suspicious hypersensitivity cases against the medicinal product,
- In pregnancy and lactation periods,
- Less than two years of children,
- In patients with severe liver impairment,
- Avoid the administration of the drug in patients with bronchorrhea and reduced mucociliary function (Kartagener syndrome, ciliary dyskinesia)
- Less than two years old children

4.4. Special warnings and precautions for use

- In severe renal impairment cases (creatinine clearance <35 ml/min), it must be administered by considering the benefit-risk rate.
- Levodropropizine pharmacokinetic does not change for geriatric population. Average dose adjustment is not necessary for old patients. However, dosage of PULMOREST FORT should be determined carefully for the geriatric patients.
- Cough medicines treats only symptoms and it should be administered until the treatment of underlying pathology is ensured and/or until the precipitating cause is determined. For this reason, PULMOREST FORT should not be used for long term treatment. In any case, if after short term of therapy, cough is still present, ask for the physician's advice.
- Contraindicated in less than two years old children. It is not recommended in children under the age of 6
- Despite the fact that no interaction with benzodiazepines was observed in the clinical studies, hypersensitive patients especially administering sedative medicines should be careful while using (See section 4.5).
- Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine.
- Methyl parahydroxybenzoate and propyl parahydroxybenzoate in PULMOREST FORT may possibly cause delayed allergic reactions.

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

Despite the fact that no interaction with benzodiazepines was observed in the clinical studies, hypersensitive patients especially administering sedative medicines should be careful while using. Animal pharmacology studies have demonstrated that Levodropropizin does not potentiate the pharmacological effect of substances acting on the central nervous system (eg. benzodiazepines, alcohol, phenytoin, imipramine). In animals, the product does not modify the activity of oral anticoagulants, such as warfarin, nor does it interfere with the hypoglycaemic effect of insulin. In human pharmacology studies, combination with benzodiazepine does not modify the EEG pattern. Caution is necessary in case of the concomitant intake of sedative drugs in particularly sensitive subjects. Clinical studies do not show any interaction with drugs for the treatment of bronchopulmonary pathologies, such as beta-2-agonists, methylxantines and derivatives, corticosteroids, antibiotics, mucoregulators and antihistamines.

Additional information related to special populations

No interactions have been reported.

Pediatric population:

No interactions have been reported.

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

According to animal toxicology study, 24mg/kg dosage causes increasing body weight and delayed embryonic development. Levodropropizine crosses the rat placenta barrier. It has been proven that it has detrimental effect on fetus in human. For this reason, it should not be administered during pregnancy period (See section 4.3).

Lactation period

According to animal toxicology study, after the medicine was applied to rats, levodropropizine extracts into its 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. An individual case has been reported of tonic-clonic convulsions and an attack of petit mal.

Eye Disorder:

An individual case has been reported of mydriasis. The other individual case has been reported vision loss to either the left or right side. For both cases, side effects are disappeared after discontinued treatment.

Cardiovascular disorders

Very rare: Palpitations, tachycardia, arrhythmias. One case of cardiac arrhythmia (atrial bigeminism) has been reported.

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.

One case of cholestatic hepatitis has been reported as well as one case of hypoglycaemic coma in an old female patient receiving concomitant oral hypoglycaemics.

Skin and subcutaneous tissue disorders

Very rare: Allergic skin rashes, urticaria, erythema, exanthema, pruritus, angioedema, itching. An individual case has been reported of epidermolysis with fatal outcome.

Musculoskeletal, connective tissue and bone disorder

Very rare: Lower extremities asthenia and weakness

General Disorder and Administration Site Conditions:

Very Rare: General malaise, general edema, asthenia.

An individual case has been reported of sleepiness, hypotonia and vomiting in a newborn after the intake of Levodropropizin on behalf of the lactating mother. Symptoms appeared after feed and spontaneously solved by discontinuing breast lactation for some feeds.

some feeds. One individual case of epidermolysis occurring abroad in an old female patient submitted to multiple treatments had fatal outcome.

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 side effect was observed after the administration of a single dose up to 240 mg or 120 mg dosage three times per day for 8 days. In case of an overdose, a dull and temporary tachycardia may occur. Only one case of overdose is known in a 3 yearold child treated with a 360 mg daily dose of Levodropropizin. The patient showed not severe abdominal pain and vomiting that solved without consequences. In case of overdose with evident clinical signs, immediately set up a symptomatic therapy and adopt the usual emergency measures (gastric lavage, active coal, parenteral liquid, etc.), if needed.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic class: Other cough suppressant drugs

ATC code: R05DB27

Antitussive effect of Levodropropizine is at tracheobronchial level and in peripheral type. It has inhibitor effect on C-fibrils and inhibits the neuropeptide oscillation.

Levodropropizin is a molecule obtained through stereospecific synthesis and chemically corresponds to S(-)3-(4-phenyl-piperazin-1-il)-propan-1.2-diol.

It is a drug provided with a mainly peripheral tracheobronchial antitussive effect together with an antiallergic and antibronchospastic effect; in animals, it performs a local anaesthetic action.

The antitussive activity of Levodropropizin after oral administration in animals has turned out to be equal to or higher than the effect of dropropizine and cloperastine on the cough induced from peripheral stimuli, such as chemical substances, mechanical stimulation of the trachea and electrical stimulation of the vagal afference. Its activity on the cough induced from a central stimulus such as the electric stimulation of the trachea in the cavy is by about 10 times lower than that of codeine while the potency ratio between the two drugs is included between 0,5 and 2 in peripheral stimulation tests such as citric acid, ammonium hydrate and sulphuric acid tests.

Levodropropizin is not active when given intracerebroventricularly in the animal. This suggests that the antitussive activity of the compound is due to a peripheral mechanism and not to an action on the central nervous system. The comparison between the efficacy of Levodropropizin and codeine given orally and by aerosol for the prevention of experimentally induced cough in the cavy further confirms the peripheral site of action of Levodropropizin; indeed, Levodropropizin is equally active or more potent than codeine by aerosol but twice less potent than codeine after oral administration.

As for the mechanism of action, Levodropropizin carries out its antitussive activity through an inhibitory action on C-fibres. In particular, Levodropropizin has turned out to be able to inhibit “in vitro” the release of sensor neuropeptides from C-fibres. In anaesthetized cats, it markedly reduces the activation of C-fibres and abolishes associated reflexes.

Levodropropizin is significantly less active than dropropizine on oxotremorine-induced tremors and pentamethylentetrazole-induced convulsions and in modifying the spontaneous motility in the mouse.

Levodropropizin does not replace naloxone from opioids receptors in the brain of rats; it does not modify the morphine-induced abstinence syndrome and the discontinuation of its administration is not followed from the onset of dependence behaviours.

Levodropropizin does not cause either respiratory function depression or appreciable cardiovascular effects in the animal, nor does it induce constipation effects. Levodropropizin acts on the bronchopulmonary system inhibiting the bronchospasm induced from histamine, serotonin and bradykinine. The drug does not inhibit the bronchospasm induced from acetylcholine thus demonstrating the absence of anticholinergic effects. In the animal, ED₅₀ of the antibronchospastic activity is comparable with the antitussive activity one.

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

Many experimental evidences demonstrate the clinical efficacy of Levodropropizin in reducing the cough of different etiology, such as cough associated with bronchopulmonary carcinoma, cough associated with infections of the upper and lower airways and pertussis. The anticough action is generally comparable with that of centrally active drugs in comparison to which Levodropropizin has a better tolerability profile mainly as for central sedative effects.

At therapeutic doses, Levodropropizin does not modify in humans either the EEG pattern or the psychomotorial ability. No modifications of cardiovascular parameters were pointed out in healthy volunteers receiving up to 240 mg of Levodropropizin.

This drug does not depress either the respiratory function or the mucociliary clearance in humans. In particular, a recent study has demonstrated that Levodropropizin has no depressive effects on the central breath regulation systems in patients with chronic respiratory failure, both in conditions of spontaneous breathing and during hypercapnic ventilation.

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 75 ml honey colored bottle containing 75 ml syrup, with a measuring spoon (on 1,5ml, 2,5ml, and 5ml notches) for 5 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

228/78

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorization: 31.12.2010

Date of the latest renewal: -

10. DATE OF REVISION OF THE SPC

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