SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
DROPOLEV 30 mg + 2 mg/5 ml SYRUP

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 5 ml (1 spoon) syrup contains,

Active substance:

Levodropropizine	30 mg
Chlorpheniramine maleate	2 mg

Excipients:

Sucrose	1750.0 mg
Methyl paraben sodium	6.5 mg
Propyl paraben sodium	1.0 mg
Ponso 4R	0.5 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Syrup.
Red clear solution with aromatic odor.

4. CLINICAL PARTICULARS
4.1. Therapeutic indications
It is indicated for the symptomatic treatment of dry cough (Non-productive cough) due to various causes.

4.2. Posology and method of administration
Posology/frequency of administration and duration:

Adults:
Apply 10 ml syrup (2 spoons) three times a day with an interval of at least 6 hours.

Children:
It is not recommended to use in children under 12 years.

5 ml three times per day in patients weighing 20-30 kg (one full spoon)
10 ml three times per day in patients over 30 kg (two full spoons)

The drug should be taken until the cough disappears or according to the advice of a physician provided that maximum 7-day treatment period is not exceeded. If the symptoms do not disappear within this period, the medication should be temporarily discontinued and a physician should be consulted.

Route of administration:
For oral use only.

Although any information that there is effect on the absorption when the drug is taken with food is not available, it is advisable to take the medicine a time before or after the meal.

It can be used with a measuring spoon.

Additional information on special populations:
Renal/Hepatic failure:
It should be used with caution considering the benefit-risk ratio in cases of the severe renal failure (creatinine clearance <35 ml/min.) It leads to sedation in severe liver disease. It should not be used in patients with liver failure.

Pediatric population: It is not recommended to use in children under 12 years.

Geriatric population: The dose of DROPOLEV should be determined with caution in elderly patients.

4.3. Contraindications
It is contraindicated in cases of known or suspected hypersensitivity to the drug, during pregnancy and lactation, in patients with severe hepatic failure, in cases such as kartagener's syndrome associated with bronchorrhea and decrease in mucociliary clearance mechanism or ciliary dyskinesia.

It is not recommended to use under 12 years.

DROPOLEV is contraindicated in patients using monoamine oxidase inhibitor (MAOI) within the last 14 days

4.4. Special warnings and precautions for use
It should be used with caution considering the benefit-risk ratio in cases of the severe renal failure (creatinine clearance <35 ml/min.). Cough medicines provide symptomatic treatment and should not be used until the treatment of the underlying pathology is provided and/or precipitating cause is detected. Therefore, DROPOLEV should not be used in long-term treatments. If there is no significant result after a short-term treatment, the doctor should be consulted

As the pharmacokinetic profile of Levodropropizine has not change significantly in elderly patients, dose adjustment or change in time between applications may not be necessary in elderly patients. However, it is clearly known that the sensitivities of elderly patients to many medicines have changed; special attention must be paid when levodropropizin is administered in this group. It should be avoided in the following cases:

- Arrhythmia
- Epilepsy
- Severe hypertension
- Cardiovascular disease
- Prostate hypertrophy
- Liver failure
- Glaucoma
- Bronchitis, bronchiectasis, asthma
- Overactive thyroid dysfunction.

Children and the elderly are more susceptible to neurological anticholinergic side effects and paradoxical excitation (such as increased energy, restlessness, irritability).

As DROPOLEV contains chlorpheniramine maleate which may increase the effect of alcohol, it should be avoided with alcohol. Chlorpheniramine maleate should not be used with antihistamines indicated in treatment of cough and cold.

Since it contains sucrose, patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not use this medicine.

Contains 1.75 g sucrose per dose.
This should be considered in diabetic patients.

Methyl paraben sodium and propyl paraben sodium contained in DROPOLEV may cause allergic reactions (possibly delayed).

The ponso 4R contained in DROPOLEV may cause allergic reactions.

4.5. Interaction with other medicinal products and other forms of interaction
The sedative effect increases when alcohol and classical antihistamines (sedative) are used together. Sedative interactions are more limited with non-sedated antihistamines. Topically applied antihistamines (including those administered by inhalation) do not show this type of interaction.

Some other central nervous system depressants such as anxiolytics or hypnotics may potentiate chlorpheniramine maleate and its sedative effects.

Phenytoin metabolism is inhibited by chlorpheniramine maleate, which can cause phenytoin toxicity.

The anticholinergic effects of chlorpheniramine maleate are exacerbated by the use of other anticholinergic drugs such as atropine, tricyclic antidepressants and MAOI

Additional information on special populations:
There are no interaction studies.

Pediatric population:
No interaction studies

4.6. Pregnancy and lactation
General recommendation
Pregnancy category is D.

Women with Childbearing Potential/Birth control (Contraception)
It should not be used in women with childbearing potential and an effective method of contraception should be applied

Pregnancy
A dose of 24 mg/kg was observed to cause a slight delay in body weight gain and growth. Levodropropizine can cross the placental barrier in rats and thus, since safety has not established in pregnant women and women planning to become pregnant, it is contraindicated.

There are detrimental pharmacological effects of Levodropropizine on pregnancy and/or fetus/newborn. Levodropropizine can cross the placental barrier. As it has proven to be detrimental effects on the human fetus, it should not be used in pregnant women.

There is no adequate information on use of chlorpheniramine in pregnant women. The potential risk for humans is unknown and use in third trimester can cause reaction in term infants or premature newborns. It should not be used in pregnancy unless absolutely necessary by a physician.

DROPOLEV is contraindicated during pregnancy.

Lactation
Levodropropizine was detected in the breast milk 8 hours after administration in mice studies. As levodropropizine passes into breast milk, it should be not used in breast-feeding women.

Sleepiness, hypotonia and vomiting are reported in the newborn after a breast-feeding woman received levodropropizine. Since symptoms occur after breastfeeding, it disappeared spontaneously after breastfeeding has discontinued.

Chlorpheniramine maleate passes into breast milk at significant amount; although it is not known that the drug has a detrimental effect on the baby at this level, it is not recommended to use. Chlorpheniramine maleate and other antihistamines may inhibit lactation

Reproductive ability / Fertility
No specific toxic effects were observed in fertility studies conducted in addition to the peri-natal and post-natal studies.

4.7. Effects on ability to drive and use machines
Drowsiness, dizziness and blurred vision which are the most serious anticholinergic properties of chlorpheniramine may prevent the patient's ability to drive and use machines. It can also cause psychomotor impairment (see Section 4.8). Very caution should be exercised during the drive and use machines. The patient should be informed about this possibility.

4.8. Undesirable effects
Adverse reactions considered to be drug related are listed below:

Frequencies are defined as follows: very common (≥ 1/10); common (≥ 1/100 to< 1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10.000 to < 1/1000); very rare (< 1/10.000), not known (cannot be estimated from available data).

Blood and lymphatic system disorders
Unknown: Hemolytic anemia, blood dyscrasia.

Immune system disorders
Very rare: Hypersensitivity reactions.
Unknown: Allergic reaction, angioedema, anaphylactic reactions.

Metabolism and nutritional disorders
Unknown: Anorexia.

Psychiatric disorders
Very rare: Nervousness, drowsiness, loss of self.
Unknown: Insomnia, Increased excitability *, anxiety, confusion*, irritability*, nightmares*, depression*.

Nervous system disorders
Very common: Sedation, somnolence.
Common: Distractibility, abnormal coordination, dizziness.
Very rare: Fatigue-asthenia, weakness, lethargy, headache, vertigo, tremor, paresthesia.
Tonic-clonic convulsions and petitmal attacks were reported in one case.

Eye disorders
Mydriasis was reported in one case and bilateral loss of vision was reported in another case. In both cases the reaction were resolved after discontinuation of the drug
Unknown: Blurred vision.

Ear and inner ear disorders
Unknown: Tinnitus.

Cardiac disorders
Very rare: Palpitation, tachycardia.
Unknown: Arrhythmia.

Vascular disorders
Very rare: Hypotension.
Atrial bigeminal beat was reported in one case.

Respiratory, thoracic and mediastinal disorders
Unknown: Darkening of bronchial secretions.

Respiratory, thoracic and mediastinal disorders
Very rare: Dyspnea, cough, edema in the respiratory tract.
Unknown: Darkening of bronchial secretions.

Gastrointestinal diseases
Common: Constipation, vomiting, dry mouth.
Very rare: Nausea, heartburn and pain, dyspepsia, diarrhea. Glossitis and aphthous were reported in two cases.

Cholestatic hepatitis was reported in one case and hypoglycemic coma was observed in elderly patients using oral hypoglycemics at the same time.

Hepatobiliary system disorders
Unknown: Hepatitis, jaundice.

Skin and subcutaneous tissue disorders
Very rare: Allergic skin rash, urticaria, erythema, exanthema, itching, angioedema.
Unknown: Exfoliative dermatitis, redness, photosensitivity.
A case of epidermolysis resulting in death has also been reported.

Musculoskeletal and Connective Tissue Disorders
Very rare: Asthenia and weakness in lower extremities.
Unknown: Muscle twitching and muscle weakness.

Kidney and Urinary Tract Disorders
Rare: Urinary retention.
General disorders and administration site conditions
Common: Exhaustion.
Very rare: Allergic and anaphylactic reactions. General malaise. Edema, syncope and asthenia have been reported rarely.
Unknown: Chest pain and tightness.

* Children and the elderly are more susceptible to neurological anticholinergic side effects and paradoxical excitation (such as increased energy, restlessness, irritability).

4.9. Overdose
No serious side effects were observed following the administration of a single dose of up to 240 mg of the drug or of up to 120 mg t.i.d. for 8 days.

No cases of levodropropizine overdose have been reported. However a mild, temporary tachycardia may be seen in the case of a possible overdose. It is known only that overdose cases are seen in a 3-year-old child treated with 360 mg daily dose of levodropropizine. Non-severe abdominal pain and nausea observed in the patient improved without causing any problems. In the case of an overdose, the measures to be taken against poisoning include gastric lavage, administering activated charcoal, initiation of parenteral fluid therapy. There is no specific antidote

If 3-5 times of the daily dose of chlorpheniramine maleate is taken orally, it leads to intoxication. Children are more susceptible to anticholinergic toxic effects of antihistamine drugs than adults. Signs and symptoms are sedation, paradoxical excitation in CNS, toxic psychosis, convulsions, apnea, anticholinergic effects, dystonic reactions, arrhythmia, and cardiovascular collapse. Its lethal dose is between 25 and 50 mg / kg.

Basic and advanced life support should be given if necessary. If there is pulseless ventricular fibrillation, defibrillation is applied. Because signs and symptoms of poisoning may be delayed due to the anticholinergic effect, patients without symptoms should be monitored for at least 6-8 hours. Hypotension and arrhythmias should be treated aggressively. It should be ready against the coma, convulsion, hyperthermia and ventricular tachycardia during monitoring period.

5. PHARMACOLOGICAL PROPERTIES
5.1. Pharmacodynamic Properties
Pharmacotherapeutic group: Other cough suppressants, combinations
ATC Code: R05DB20

Levodropropizine has a peripheral tracheobronchial antitussive effect. It has an inhibitory impact on the C fibers and inhibits neuropeptide secretion.

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 guinea pigs 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 guinea pigs further confirms the peripheral site of action of Levodropropizin. Actually, 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. Levodropropizine acts on the bronchopulmonary system inhibiting the bronchospasm induced from histamine, serotonine and bradychinine. 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 receving 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

Chlorpheniramine maleate is an alkylamine derivative, potent antihistamine with an anticholinergic activity. As it is a H1 receptor antagonist, it temporarily relieves allergic symptoms such as nasal discharge, watery eyes, sneeze of the allergic diseases in upper respiratory tract. It is an antihistamine with good therapeutic effect. Antihistamines give symptomatic relief and relief continues as long as drug intake continues

5.2. Pharmacokinetic properties

Absorption:

After oral administration, the bioavailability is found to be over 75%. The plasma protein-binding capability is found to be low (11-14%)

Chlorpheniramine maleate is well absorbed following oral administration; its effect starts in 15-60 minutes and reaches the maximum in 3-6 hours.

Distribution:

Levodropropizine is absorbed rapidly after oral intake in humans and is rapidly distributed in the body. Chlorpheniramine maleate is approximately 70% bound to plasma proteins. It shows a wide distribution in the body including central nervous system. It crosses the placenta and is excreted into the breast milk.

Biotransformation:

There are no data about that levodropropizine is metabolized significantly in the liver or other body areas. Chlorpheniramine maleate is rapidly and extensively metabolized. First, it is metabolized in the gastrointestinal mucosa and then, it undergoes the first-pass metabolism in the liver. N-dealkylation results in different metabolites.

Elimination:

The plasma elimination half-life of levodropropizine is about 1 to 2 hours. It is primarily excreted in the urine. The active substance is excreted as both unchanged and conjugated or free levodropropizine and conjugated p-hydroxy levodropropizine metabolites. Urinary excretion of this substance and its metabolites within 48 hours is about 35% of the administered dose. The results of the repeated dose studies showed that an 8-day treatment (t.i.d.) does not alter the characteristics of the drug excretion thus, allowing to exclude accumulation or metabolic autoinduction in the body. Chlorpheniramine maleate is excreted via the kidneys as metabolites within 24 hours.

5.3. Preclinical safety data

Oral acute toxicity is 886.5 mg/kg, 1287 mg/kg and 2492 mg/kg in rats, mice and guinea pigs, respectively. The therapeutic index in the guinea pigs, calculated as LD50/ED50 ratio after oral administration is included between 16 and 53 according to the experimental model of cough induction. Toxicity tests for repeated oral administrations have shown that the daily dose without toxic effect corresponds to 24 mg/kg

No additional information is available for chlorpheniramine maleate.

6. PHARMACEUTICAL PROPERTIES

6.1. List of excipients

Methyl paraben sodium
Propyl paraben sodium
Sucrose
Citric acid monohydrate
Vanilla flavor

Raspberry flavor
Ponso 4R
Deionized water

6.2. Incompatibilities
Not applicable

6.3. Shelf life
36 months

6.4. Special precautions for storage
Store at room temperature below 25ºC protected from light.

6.5. Nature and contents of container
DROPOLEV is marketed in amber colored glass bottle (Type III) closed with high density polyethylene (HDPE) cap and low density polyethylene seal.

Each cardboard box contains one bottle and one spoon of 5 ml.

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 Packaging and Packaging Waste".

7. MARKETING AUTHORIZATION HOLDER
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8. MARKETING AUTHORISATION NUMBER(S)
2014/657

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
Date of first authorization: 09.09.2014
Date of latest renewal: 23.01.2020

10. DATE OF REVISION OF THE TEXT
15.05.2020