Levodropropizine

Levopront®

30mg/5mL Syrup

Cough Suppressant

Levodropropizine is new compound with an essentially peripheral action on the tracheobronchial tree.

FORMULATION

Each 5 mL contains:

Levodropropizine ..... 30 mg

INDICATIONS

For the symptomatic relief of cough.

PHARMACODYNAMICS:

Levodropropizine is obtained by stereospecific synthesis and has the chemical formula S(-)3-(4-phenyl-piperazine-1-yl)-propan-1,2-diol. It is an antitussive with a primarily peripheral tracheobronchial action, associated with antiallergic and antibronchospastic activity; in animals it also has a local anaesthetic effect. In animals, levodropropizine's antitussive activity after oral administration has been observed to be equal or superior to dropropizine and cloperastine on cough induced by peripheral stimuli such as chemical substances, mechanical stimulation of the trachea and electrical vagal afferent stimulation. Its activity on cough induced by central stimulation such as the electrical stimulation of the trachea in guinea pigs is approximately one tenth that of codeine, whereas the potency ratio between the two medicinal products is between 0.5 and 2 in peripheral stimulation tests, such as those using citric acid, ammonium hydrate and sulphuric acid. Levodropropizine is not active when administered via the intracerebroventricular route in animals. This fact suggests that the compound's antitussive activity is due to a peripheral mechanism, rather than an action on the central nervous system. The comparison between the efficacy of levodropropizine and that of codeine, when administered via the oral route and using a nebuliser, in preventing experimentally-induced cough in guinea pigs, provides further confirmation of levodropropizine's peripheral site of action; in fact, levodropropizine is equally potent to or more potent than codeine when administered by nebuliser and, when administered via the oral route, it is half as potent as codeine.

As regards its mechanism of action, levodropropizine exerts its antitussive effect through the inhibition of the C fibres. In particular, levodropropizine was seen to inhibit the release of neuropeptide sensors by the C fibres "in vitro". Moreover, in anaesthetised cats, it significantly reduces C fibre activation and abolishes the associated reflexes.

Levodropropizine is significantly less active than dropropizine on oxotremorine-induced tremors and on pentamethylene tetrazole-induced seizures and in modifying spontaneous motility in mice. Levodropropizine does not displace naxolone from the opioid receptors in rat brains; it does not affect morphine withdrawal symptoms and its withdrawal is not followed by addiction behaviour. In animals, levodropropizine does not cause respiratory function depression or significant cardiovascular effects, nor does it cause constipation. Levodropropizine acts on the bronchopulmonary system inhibiting histamine-, serotonin-, and bradykinin-induced bronchospasm. The product does not inhibit acetylcholine-induced bronchospasm, thereby demonstrating the absence of anticholinergic effects. In animals, the ED50 of antibronchospastic activity is similar to that of the antitussive activity. In healthy volunteers, a 60 mg dose of medicinal product reduced cough induced by citric acid administered by nebuliser for at least six hours. A number of trial experiences have shown the clinical efficacy of levodropropizine in reducing cough with diverse aetiologies, including cough associated with lung cancer, upper and lower respiratory tract infections and whooping cough. Its antitussive action is generally speaking similar to that of medicinal products with a central action, compared to which levodropropizine has a better tolerability profile, particularly as regards central sedative effects. At therapeutic doses levodropropizine does not cause EEG alterations or affect psychomotor abilities in humans. No alterations were observed in the cardiovascular parameters of healthy volunteers treated with doses of up to 240 mg of levodropropizine. The medicinal product does not depress respiratory function or mucociliary clearance in humans. Specifically, one recent study showed that levodropropizine has no depressive effects on the central respiratory regulation systems in patients with chronic respiratory insufficiency, both in conditions of spontaneous respiration and during hypercapnic ventilation.

PHARMACOKINETICS:

Pharmacokinetics studies have been conducted in rats, dogs and humans. Absorption, distribution, metabolism and excretion were very similar in the three species considered, with an oral bioavailability of over 75%. The recovery of radioactivity after oral administration of the product was 93%. Its binding with human plasma proteins is negligible (11-14%) and similar to that observed in dogs and rats. Levodropropizine is rapidly absorbed in humans after oral administration and it is rapidly distributed throughout the body. It has a half-life of about 1-2 hours. the product is excreted primarily in urine as unmodified product and its metabolites (conjugated levodropropizine and free and cojugated p-hydroxy levodropropizine). Within 48, hours, approximately 35% of the administered dose is excreted in uring and the aforesaid metabolites. Repeated administration test show that an 8-day course of treatment (t.i.d.) does not alter the medicinal product's absorption and elimination profile, making it possible to rule out accumulation and metabolic auto-induction phenomena. There are no significant changes to the pharmacokinetic profile in children, the elderly or those with mild or moderate renal insufficiency.

DOSAGE AND ADMINISTRATION

•Adults and children over 12 years of age:
Two teaspoons/ 10mL (equivalent to 60 mg of levodropropizine) up to 3 x daily at intervals of at least 6 hours.
•Children over 2 years of age:
The pediatric dose is 1 mg/kg 3 x daily, for a total daily dose of 3 mg/kg at intervals of at least 6 hours.

For convenience, the following approximate dosages can be used:
10-20 kg body weight: 3 mL up to 3 x daily
20-30 kg body weight: 5 mL up to 3 x daily

The preparation is administered orally.
The medication should be taken between meals, since the effect of concomitant food consumption has not yet been determined.

TREATMENT DURATION

The treatment should be taken until the cough clears up, or as directed by a physician, for a period not to exceed seven days. If symptoms persist after this period, treatment should be stopped and a physician should be consulted.

DRUG INTERACTIONS

No interactions with benzodiazepines were observed during clinical trials,however, care should be taken when sedative drugs are simultaneously administered to particularly sensitive individuals.

CONTRAINDICATION

Hypersensitivity to the active ingredient or to any of the excipients. The medicinal product should not be administered to patients with bronchorrhea and reduced mucociliary clearance (Kartagener syndrome, ciliary dyskinesia). Do not administer to children under two years of age.

WARNING AND PRECAUTIONS FOR USE

- Care should be taken for patients with serious renal insufficiency.
- Notice to diabetics: 10 mL of Levopront contains 3.5 g sucrose (equal to 0.3 bread units)
- The safety and efficacy of levodropropizine in children less than 24 month has not yet been established.
- Drivers of vehicles and machine operators are warned of the possibility of drowsiness with the use of this drug.

PREGNANCY AND LACTATION

Teratogenesis, reproductive, fertility and peri- and post-natal studies have not shown any specific toxic effects. However, since in toxicology studies on animals at the dose of 24 mg/kg a slight delay was observed in weight gain and growth and as levodropropizine passes through the placental barrier in rats, the use of the medicinal product is contraindicated in women who are pregnant or intend to start a pregnancy, since there is no evidence on its safety of use. Studies on rats suggest that the medicinal product can bedetected in breast milk up to 8 hours after administration. Use of the medicinal product during pregnancy is therefore contraindicated.

ADVERSE DRUG REACTION

The following side effects sometimes occur:
- Gastrointestinal tract:
  - -nausea
  - -vomiting
  - -heartburn
  - -abdominal discomfort
  - -diarrhea
- Central nervous system
  - -exhaustion, faintness
  - -somnolence, clouding of consciousness (stupor)
  - -numbness
  - -dizziness
  - -headache
- Cardiovascular system
  - -palpitations
- Hypersensitivity reactions may occur in predisposed patients because Levopront contains parabens.
- Allergic skin reactions were observed in very rare cases.
- Consult your physician or the pharmacist in the event other side effects appear.

ADR STATEMENT

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph
Instruction to the patient to seek medical attention immediately at the first sign of ADR.

OVERDOSE AND TREATMENT:

No significant side effects have been reported after administration of up to 240 mg in a single administration and up to 120 mg t.i.d. for 8 consecutive days. There are known cases of overdose in children aged between 2 and 4 years. These are cases of accidental overdose, all solved without consequences. In most cases, patients have experienced abdominal pain and vomiting and in one case, after taking 600 mg of Levodropropizine, a patient experienced excessive sleep and decreased oxygen saturation. In the event of overdose with evident clinical manifestations, immediately introduce symptomatic therapy and apply the usual emergency measures (gastric irrigation, activated charcoal, parenteral fluid administration, etc.), as appropriate.

PRESCRIPTION STATUS

This product is sold only with a physician's prescription.

ATTENTION: DO NOT USE THE DRUG AFTER THE EXPIRATION DATE INDICATED ON THE BOX

STORAGE CONDITIONS

Store at a temperature not exceeding 30°C. Keep away from children.

AVAILABILITY

Type III Amber Glass Bottle x 60mL and 120mL (Box of 1's)

CAUTION

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

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