SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
Levotuss 30 mg/5 ml syrup

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
100 ml of solution contain:
Active ingredient: Levodropropizine 600 mg
Excipients: saccharose, methyl-para-hydroxybenzoate, propyl-para-hydroxybenzoate,
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Syrup

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Symptomatic therapy of cough

4.2 Posology and method of administration
The package includes a measuring glass with 3, 5 and 10 ml notches.
To open the bottle hardly press the cap and turn anticlockwise.
Posology
Adults: 10 ml of syrup up to 3 times daily with at least 6-hour-intervals.
Children: 10-20 kg 3 ml 3 times daily; 20-30 kg 5 ml 3 times daily.
Treatment should be continued until cough disappears or according. In any case, if after 2 weeks of therapy, cough is still present, it is advisable to discontinue treatment and ask for the physician's advice. Indeed, cough is a symptom and its causal pathology should be studied and treated**.**

Paediatric population
Levotuss syrup should not be used in children below 2 years of age (see paragraph 4.3).

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. Avoid the administration of the drug in patients with bronchorrhea and reduced mucociliary function (Kartagener syndrome, ciliary dyskinesia). Pregnancy and lactation (see 4.6).
Levotuss syrup is contraindicated in children below 2 years of age.

4.4 Special warnings and precautions for use
The observation that the pharmacokinetic profiles of Levodropropizine are not markedly altered in old subjects suggests that dose adjustments or modifications of the intervals between administrations may not be required in elderly persons. In any case, being evident that the sensitivity to several drugs is altered in old patients, special caution is necessary when administering Levodropropizine to old patients.
Caution is recommended in patients with severe renal failure (creatinine clearance < 35 ml/min).
Caution is also recommended for the concomitant intake of sedative drugs in particularly sensitive subjects (see 4.5).
The drug contains 4g of sucrose per dose (10 ml): patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine. This should be taken into account in patients with diabetes mellitus.
The drug contains methyl-para-hydroxybenzoate and propyl-para-hydroxybenzoate that are known for the possibility of causing urticaria. Para-hydroxybenzoates may generally cause delayed reactions such as contact dermatitis and rarely immediate reactions with urticaria and bronchospasm (tightening of the bronchi causing difficult breathing).
Anti-cough drugs are symptomatic and must be used only when waiting for the diagnosis of the triggering cause and/or the effect of the therapy of the underlying pathology.

In the absence of information about the effect of the intake of food on drug absorption, it is advisable to take the drug away from meals.
Levotuss syrup does not contain gluten and may thus be given to patients suffering from celiac disease.

4.5 Interactions with other medicinal products and other forms of interaction
Animal pharmacology studies have demonstrated that Levodropropizine 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, the combination with benzodiazepines does not modify the EEG-pattern. Caution is necessary in case of the concomitant intake of sedative drugs in particularly sensitive subjects (see 4.4).
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.

4.6 Fertility, pregnancy and lactation
Teratogenesis, reproduction and fertility studies as well as peri- and post-natal studies did not reveal any specific toxic effect.
Nevertheless, as in animal toxicology studies with the 24 mg/kg dose a mild delay in the body weight increase and in growth has been observed and as Levodropropizine is able to cross the placental barrier in the rat, the drug is contraindicated in women wanting to get pregnant or already pregnant as its safety of use is not documented (see 4.3). Studies in rats show that the drug can be found in the mother's milk until 8 hours after administration. Thus, the drug is contraindicated during lactation.

4.7 Effects on ability to drive and use machines
Studies have not been performed on the ability to drive and/or the use of machines. Nevertheless, as the product may rarely cause sleepiness (see 4.8) caution must be used in patients who intend to drive or use machines, informing them about this possibility.

4.8 Undesirable effects
During the treatment with Levodropropizine palpitations, tachycardia, nausea, vomiting, diarrea, erythema could occur. The adverse reactions reported as serious are urticaria and anaphylactoid reaction.
The most reactions occur after the administration of Levodropropizine are not serious and the symptoms has been solved stopping the therapy and, in some cases, with a special pharmacological treatment.

The observed adverse reactions (incidence not known) are the following:

Eye disorders
Mydriasis, bilateral blindness
Immune system disorders
Allergic and anaphylactoid reactions, eyelid oedema, angioneurotic oedema, urticaria.
Psychiatric disorders
Irritability, sleepiness, personality change or personality disorder.
Neurological disorders
Syncope, dizziness, vertigo, tremors, paresthesia, tonic-clonic convulsion. An individual case has been reported of tonic-clonic convulsions and an attack of petit mal, coma hypoglicemic.
Cardiac disorders
Palpitations, tachycardia, atrial bigeminism.
Vascular disorders
Hypotension
Respiratory, thoracic and mediastinal disorders

Dyspnoea, cough, oedema of the respiratory tract.
Gastrointestinal disorders: gastric pain, abdominal pain, nausea, vomiting, diarrhoea.
Hepatobiliary disorders
Cholestatic hepatitis
Skin and subcutaneous tissue disorders
Urticaria, erythema, exanthema, itching, angioedema, skin reactions, glossitis and aphthous stomatitis Epidermolysis.
Musculoskeletal and connective tissue disorders
Weakness of lower limbs.
General disorders and administration site conditions
General malaise, generalised oedema, asthenia.

Pediatric population
A case of drowsiness, hypotonia and vomiting was reported in an infant after levodropropizine was taken by a nursing mother. Symptoms appeared after feeding and resolved spontaneously when breastfeeding was suspended for a few feedings.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 the national ADR reporting website: www.medicinesauthority.gov.mt/adrportal

4.9 Overdose
No significant side effects have been reported after the administration of a single dose of up to 240 mg of the drug and of up to 120 mg t.i.d. for 8 consecutive days. There were no reports of significant adverse effects after administering up to 240 mg of the drug in a single dose 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 resolved without sequelae. In most cases, the patients experienced abdominal pain and vomiting and in one case, after taking 600 mg of levodropropizine, the patient experienced excessive sleep and decreased oxygen saturation. In case of overdose with obvious clinical manifestations, symptomatic treatment should be immediately instituted and the usual emergency measures applied (gastric lavage, activated charcoal meal, parenteral administration of fluid, etc..), if applicable.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic class: cough and cold preparation: cough suppressant, excl. combinations with expectorans: other cough suppressant.
ATC code: R05DB27
Levodropropizine 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 Levodropropizine 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.

Levodropropizine 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 Levodropropizine 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 Levodropropizine; indeed, Levodropropizine 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, Levodropropizine carries out its antitussive activity through an inhibitory action on C-fibres. In particular, Levodropropizine 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.
Levodropropizine is significantly less active than dropropizine on oxotremorine-induced tremors and pentamethylentetrazole-induced convulsions and in modifying the spontaneous motility in the mouse.
Levodropropizine 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.
Levodropropizine 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 Levodropropizine 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 Levodropropizine has a better tolerability profile mainly as for central sedative effects.
At therapeutic doses, Levodropropizine 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 Levodropropizine.
This drug does not depress either the respiratory function or the mucociliary clearance in humans. In particular, a recent study has demonstrated that Levodropropizine 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
Pharmacokinetic studies have been performed in rats, dogs and humans. The absorption, distribution, metabolism and secretion of the drug have turned out to be very similar in the three species considered with an oral bioavailability higher than 75%. The radioactivity recovery after oral administration of the product has achieved 93%.
The binding with human plasma proteins is negligible (11-14%) and comparable with the one observed in dogs and rats.
Levodropropizine is rapidly absorbed in humans after oral administration and is rapidly distributed in the organism. Half-life is of about 1-2 hours. The product is mainly secreted in urines as unaltered product and its metabolites (conjugated Levodropropizine and free and conjugated p-hydroxy-Levodropropizine). The urinary secretion of the product and above metabolites in 48 hours is equal to about 35% of the administered dose. Repeated administration tests show that an 8-day- treatment (t.i.d.) does not alter the absorption and elimination profile of the drug, thus allowing to exclude accumulation and metabolic self-induction phenomena.
There are no significant modifications of the pharmacokinetic profile in children, old patients and patients with mild or moderate renal failure.

5.3 Preclinical safety data

Oral acute toxicity is 886.5 mg/kg, 1287 mg/kg and 2492 mg/kg in rats, mice and cavies, respectively. The therapeutic index in the cavy, calculated as DL50/DE50 ratio after oral administration is included between 16 and 53 according to the experimental model of cough induction. Toxicity tests for repeated oral administrations (4-26 weeks) have shown that the daily dose without toxic effect corresponds to 24 mg/kg.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Saccharose, methyl-para-hydroxybenzoate, propyl-para-hydroxybenzoate, citric acid monohydrate, sodium hydroxide, cherry aroma, purified water

6.2 Incompatibilities

Not pertinent

6.3 Shelf-life

3 years
The expiry date refers to an undamaged and correctly stored product.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Dark glass bottle to 220 ml, containing 200 ml of solution, sealed with plastic child-proof cap, and measuring glass of neutral PP

6.6 Special precautions for disposal

No particular instruction

7. MARKETING AUTHORIZATION HOLDER

Dompé farmaceutici spa – Via San Martino 12 - Milan

8. MARKETING AUTHORIZATION NUMBER

MA118/00401

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

03-01-2007/23-03-2012

10. DATE OF REVISION OF THE TEXT

12th February 2019