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, see 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. 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 to the physician's prescription. 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. **4.3 Contraindications** Hypersensitivity to the active ingredient or to any excipient. Avoid the administration of the drug in patients with bronchorrhea and reduced mucociliary function (Kartagener syndrome, ciliary dyskinesia). Pregnancy and lactation (see 4.6). **4.4 Special warnings and special precautions for use** The observation that the pharmacokinetic profiles of Levodropropizin 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 Levodropropizin to old patients. The effect of the administration of the product to children younger than 24 months has not been studied completely and in any case the drug should be used with caution in such 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. 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 sirup 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 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, 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 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 Levodropropizin 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**. The experience drawn from the commercialization of products containing Levodropropizin in more than 30 countries worldwide points out that undesirable effects occur very rarely. Basing on the estimate of patients exposed to Levodropropizin derived from the number of sold packagings and considering the number of spontaneous communications, less than one patient out of 500,000 has shown adverse reactions. Most reactions are not severe and symptoms resolved after therapy discontinuation and, sometimes, after specific pharmacological treatment. The following very rare adverse reactions (incidence < 1/10,000) have been observed: Skin and subcutaneous tissue disorders: urticaria, erythema, exanthema, itching, angioedema, skin reactions. An individual case has been reported of epidermolysis with fatal outcome. Gastrointestinal disorders: gastric and abdominal pain, nausea, vomiting, diarrhoea. Two individual cases have been reported of glossitis and aphthous fever, respectively. One case of cholestatic hepatitis has been reported as well as one case of hypoglycaemic coma in an old female patient receiving concomitant oral hypoglycaemica. General disorders: allergic and anaphylactoid reactions, general malaise. Individual cases have been reported of generalized edema, syncope and asthenia. Neurological disorders: dizziness, vertigo, tremor, paresthesia. An individual case has been reported of tonic-clonic convulsions and an attack of petit mal. Cardiovascular disorders: palpitations, tachycardia, hypotension. One case of cardiac arrhythmia (atrial bigeminism) has been reported. Psychiatric disorders: irritability, sleepiness, depersonalization. Respiratory disorders: dyspnoea, cough, edema of the respiratory tract. Muscularskeletal, connective tissue & bone disorders: asthenia and weakness of lower limbs. Few cases have been reported of palpebral edema, most of which to be referred to angioneurotic edema, considering the concomitant presence of urticaria. An individual case has been reported of mydriasis as well as one case of loss of the bilateral visual faculty. In both cases, the reactions resolved after drug discontinuation. 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. Adverse reactions have been severe occasionally, only. They include some cases of skin reactions (urticaria, itching), the already mentioned case of cardiac arrhythmia, the case of hypoglycaemic coma as well as some allergic/anaphylactoid reactions involving edema, dyspnoea, vomiting and diarrhoea. As already mentioned, one individual

case of epidermolysis occurring abroad in an old female patient submitted to multiple treatments had fatal outcome. The drug contains methyl-para-hydroxybenzoate and propyl-para-hydroxybenzoate, 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. **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. Only one case of overdose is known in a 3 year-old 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: cough and cold preparation: cough suppressant, excl. combinations with expectorans: other cough suppressant. ATC: R05DB27 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, 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. **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. Levodropropizin is rapidly absorbed in humans after oral administration and is rapidly distributed in the organism. Hallf-life is of about 1-2 hours. The product is mainly secreted in urines as unaltered product and its metabolites (conjugated Levodropropizin and free and conjugated p-hydroxy-Levodropropizin). 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** 2 years. The expiry date refers to an undamaged and correctly stored product. **6.4 Special precautions for storage.** No special precaution for storage is foreseen. **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 Instructions for use.** No particular instruction.