SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Toceliv 2 mg/ml syrup

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of Toceliv contains:
Dextromethorphan hydrobromide ..... 2 mg

Excipient with known effect:
This medicinal product contains 260 mg of sorbitol 70% solution in each 200 ml.
This medicinal product contains 8 mg of propylene glycol in each 200 ml.
This medicinal product contains 2 mg of sodium benzoate in each 200 ml.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Syrup.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Toceliv is indicated in the symptomatic treatment of dry and irritant cough.

4.2 Posology and method of administration

Posology

Adults and children over 12 years:
- 5 to 10 ml of Toceliv with 4 hours breaks
or
- 15 ml of Toceliv with 6-8 hours breaks.
The maximum daily dose is 60 ml of Toceliv which corresponds to 120 mg of dextromethorphan hydrobromide. Do not exceed 4 daily doses (every 24 hours).

Paediatric population

Children aged between 6 and 12 years old:
- 2.5 to 5 ml of Toceliv with 4 hours breaks.
The maximum daily dose is 30 ml of Toceliv which corresponds to 60 mg of dextromethorphan hydrobromide. Do not exceed 4 daily doses (every 24 hours).
Toceliv is contraindicated in children under 6 years old.

Elderly or patients with hepatic and/or renal insufficiency:
The initial dose should be reduced for half of the recommended dose.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Patients undergoing treatment with monoamine oxidase inhibitors (MAOIs).
Asthma.
Respiratory failure.
Patients with productive cough.
Chronic obstructive pulmonary disease.
Pneumonia.
Respiratory depression.
Children under 6 years old.
Severe Hepatic Disease.

4.4 Special warnings and precautions for use

Do not exceed the indicated dose.
Patients with asthma and patients with hepatic pathology should consult the doctor before taking the medicinal product.

Do not administer to children aged less than 6 years old without medical indication.
If the symptoms persist, consult the doctor.

Before the prescription of an antitussive treatment, the possible causes of cough that require specific treatment should be considered.
This medicinal product should not be used in cases of persistent or chronic cough, as smoker's cough, asthma or emphysema, or when the cough is very productive, as it can decrease sputum and, therefore, increase the resistance of the airways.
The intake of alcoholic drinks is not recommended during treatment.
If the cough persists for more than a week or if it is accompanied by high fever, skin rashes or persistent headache, the clinical situation should be assessed.

Dextromethorphan can lead to the development of dependency. After long periods of administration, patients may develop tolerance, as well as psychic and physical dependency. Patients with tendency for abuse or dependency should only take Toceliv for short periods of time and under strict clinical monitoring.

Cases of dextromethorphan abuse and dependence have been reported. Caution is particularly recommended in adolescents and young adults as well as in patients with a history of drug or psychoactive substances abuse.

Serotonin syndrome
Serotonergic effects, including the development of a potentially life-threatening serotonin syndrome, have been reported for dextromethorphan with concomitant administration of serotonergic agents, such as selective serotonin re-uptake inhibitors (SSRIs), drugs which impair metabolism of serotonin (including monoamine oxidase inhibitors (MAOIs)) and CYP2D6 inhibitors.

Serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and gastrointestinal symptoms.

If serotonin syndrome is suspected, treatment with Toceliv should be discontinued.

Dextromethorphan is metabolised by hepatic cytochrome P450 2D6. The activity of this enzyme is genetically determined. About 10% of the general population are poor metabolisers of CYP2D6. Poor metabolisers and patients with concomitant use of CYP2D6 inhibitors may experience exaggerated and/or prolonged effects of dextromethorphan. Caution should therefore be exercised in patients who are poor metabolizers of CYP2D6 or that are taking CYP2D6 inhibitors (see also section 4.5).

Paediatric population (only for products with paediatric indication below 12 years old)
In case of overdose, severe undesirable effects may occur in children, including neurological disorders. Caregivers should be advised not to exceed the recommended dose.

Sorbitol is a source of fructose. If your doctor has told you that you (or your child) have an intolerance to some sugars or if you have been diagnosed with hereditary fructose intolerance (HFI), a rare genetic disorder in which a person cannot break down fructose, talk to your doctor before you (or your child) take or receive this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Previous or concomitant treatment with antidepressants of the MAOI type (monoamine oxidase inhibitors) can lead to the development of serotonin syndrome with the following characteristic symptoms: neuromuscular hyperactivity (tremble, clonus, myoclonus, hyperreflexia, pyramidal rigidity), autonomic hyperactivity (diaphoresis, fever, tachycardia, mydriasis) and altered mental status (agitation, excitation, confusion).

The concomitant administration of medicinal products that inhibit the enzyme system of cytochrome P450-2D6 on the liver and, as a consequence, the metabolism of dextromethorphan - namely amiodarone, quinidine, fluoxetine, haloperidol, paroxetine, propafenone, thioridazine, cimetidine and ritonavir - can increase the dextromethorphan concentration. These effects can occur if any of the medicinal products mentioned were recently administered, even if the intake has already ended.

CYP2D6 inhibitors

Dextromethorphan is metabolized by CYP2D6 and has an extensive first-pass metabolism. Concomitant use of potent CYP2D6 enzyme inhibitors can increase the dextromethorphan concentrations in the body to levels multifold higher than normal. This increases the patient's risk for toxic effects of dextromethorphan (agitation, confusion, tremor, insomnia, diarrhoea and respiratory depression) and development of serotonin syndrome. Potent CYP2D6 enzyme inhibitors include fluoxetine, paroxetine, quinidine and terbinafine. In concomitant use with quinidine, plasma concentrations of dextromethorphan have increased up to 20-fold, which has increased the central nervous system adverse effects of the agent. Amiodarone, flecainide, propafenone, sertraline, bupropion, methadone, cinacalcet, haloperidol, perphenazine and thioridazine also have similar effects on the metabolism of dextromethorphan. If concomitant use of CYP2D6 inhibitors and dextromethorphan is necessary, the patient should be monitored and the dextromethorphan dose may need to be reduced.

Alcohol can potentiate the sedative effect of Toceliv. The resulting decrease of the surveillance can make it danger to drive vehicles or use machines. Thus, the

consumption of alcoholic drinks or other alcohol containing medicinal products should be avoided.

The concomitant administration of medicinal products with suppressive effect on the central nervous system can cause mutual potentiation.
Medicinal products such as ACE inhibitors can cause cough, so before its administration a doctor should be consulted.

The following medicinal products should not be concomitantly taken with Toceliv:
- Bupropion.
- Isoniazid.
- Linezolid.
- Moclobemide.
- Pargyline.
- Procarbazine.
- Selegiline.
- Sibutramine.
- Tranylcypromine.
- Anti-inflammatory medicines (celecoxib, parecoxib or valdecoxib).
- Expectorants and mucolytics.

4.6 Fertility, pregnancy and lactation

Pregnancy
The experimental and observational studies of the clinical practice performed up to date did not reveal teratogenic effects of dextromethorphan. However, the dextromethorphan administration should be avoided during pregnancy.

Breast-feeding
Dextromethorphan is excreted in breast milk. As a consequence, the administration of this medicinal product is contraindicated during the breast-feeding period.

Fertility
There are no dextromethorphan data on fertility.

4.7 Effects on ability to drive and use machines

No effects are expected, however, if dizziness occurs do not drive or use machines.

4.8 Undesirable effects

The frequency of undesirable effects is based on the following categories of MedDRA convention on frequency:
Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (>1/1,000 to <1/100)
Rare (≥ 1/10,000 to < 1/1,000)
Very rare (<1/10,000)
Not known (frequency cannot be estimated from the available data)

Psychiatric disorders, Nervous system disorders, General disorders and administration site conditions
Uncommon: dizziness, fatigue, somnolence, vertigo, mental confusion

Very rare: fever, prolonged headaches. Cases of dependency have been reported associated with the abuse of dextromethorphan.

Musculoskeletal and connective tissue disorders
Uncommon: dystonia

Immune system disorders
Very rare: allergy (hypersensitivity)

Gastrointestinal disorders
Uncommon: nausea, vomiting and gastrointestinal disorders, constipation

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:

Portugal

Internet website: http://www.infarmed.pt/web/infarmed/submissaoram
(preferably) or using the following contacts:
Direção de Gestão do Risco de Medicamentos
Parque da Saúde de Lisboa, Av. Brasil 53
1749-004 Lisboa
Tel: +351 21 798 73 73
Line of the Medicinal Product: 800222444 (free)
E-mail: farmacovigilancia@infarmed.pt

4.9 Overdose

Symptoms and signs
Dextromethorphan overdose may be associated with nausea, vomiting, dystonia, agitation, confusion, somnolence, lethargy, nystagmus, cardiotoxicity (tachycardia, abnormal ECG, including prolongation of QTc interval), ataxia, toxic psychosis with visual hallucinations, hyperexcitability.
In case of massive overdose, the following symptoms may be seen: coma, respiratory depression and convulsions.

Treatment
- Activated charcoal can be given to asymptomatic patients that have intake excessive doses of dextromethorphan in the previous hour.
- In patients that have intake dextromethorphan and that are sedated or comatose, treatment with naloxone should be considered, in the usual doses, for the treatment of overdose with opioid agents. The administration of benzodiazepines for convulsions and benzodiazepines and external cooling measures may be used for the treatment of hyperthermia with origin in serotonin syndrome.

Cases of abuse of dextromethorphan containing medicinal products occurred, and severe adverse effects, such as anxiety, panic memory loss, tachycardia, lethargy, hypertension or hypotension, mydriasis, vertigo, gastrointestinal disorders, slurred speech, fever, tachypnoea, cerebral damage, ataxia, loss of consciousness, arrhythmias and death can occur.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Respiratory system. Cough and cold preparations. Opium alkaloids and derivatives, ATC code: R05DA09

Dextromethorphan hydrobromide is a 3-methoxy derivative of levorphanol. It has an antitussive effect, but it does not have analgesic properties, depressant properties of the respiratory function or psychomimetic properties in the therapeutic doses and a mild additive potential is given to it.
Dextromethorphan is a cough suppressor. It acts centrally in the centre of the cough, at level of the marrow cough centre, raising the threshold for the triggering of the cough.

5.2 Pharmacokinetic properties

Absorption and Distribution
Dextromethorphan pharmacokinetics changes from subject to subject. It is, however, well absorbed on the digestive tube (70% of the administered dose), and is quickly distributed in the tissues. Its degree of binding to the proteins is not known.

Metabolism
Dextromethorphan undergoes rapid and extensive first-pass metabolism in the liver after oral administration. Genetically controlled O-demethylation (CYD2D6) is the main determinant of dextromethorphan pharmacokinetics in human volunteers. A quick first passage hepatic metabolism (plasma half-life of 1.80h) explains the relatively low plasma concentrations in unmetabolized dextromethorphan. (As an example, maximum 3 nanograms per ml after the intake of 30 mg of product). Dextromethorphan is mostly metabolized in active metabolites (dexthorphan, 3-hydroxymorphinan and, with other values, 3-metoximorphinan), being later conjugated (glucuronides and sulfoconjugates). It appears that there are distinct phenotypes for this oxidation process resulting in highly variable pharmacokinetics between subjects. Unmetabolized dextromethorphan, together with the three demethylated morphinan metabolites: dextrorphan (also known as 3-hydroxy-N-methylmorphinan), 3- hydroxymorphinan and 3-methoxymorphinan have been identified as conjugated products in the urine.
The maximum plasma rate obtained by these metabolites is obtained after 2 hours. As an example, the maximum concentrations detected in plasma after intake of 60 mg of dextromethorphan are between 30 and 800 nanograms per ml for dextromethorphan and between 30 and 500 nanograms per ml for 3-hydroxymorphinan. At the effective dose (15 mg in the adult), the antitussive action of dextromethorphan begins 15 to 30 minutes after the administration and lasts 5 to 6 hours. Dextrorphan, which also has antitussive action, is the main metabolite. In some individuals, metabolism proceeds more slowly and unchanged dextromethorphan prevails in the blood and urine.

Excretion
The excretion is mainly urinary. 30 to 60% of the administered dose can be found in the 24 hours urine, essentially as conjugated derivatives of dextromethorphan (concentration: about 20 micrograms/ml, 40% of the ingested dose), of 3-hydroxymorphinan (20% of the ingested dose) and as unmetabolized (less than 10%

of the ingested dose). 3-metoximorphinan is excreted in small quantity which is difficult to evaluate with precision (less than 1% of the ingested dose).

5.3 Preclinical safety data

The experience acquired with the dextromethorphan use along the years did not lead to the appearance of teratogenic effects. There are no data available on the long term carcinogenic and mutagenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sodium saccharin
Propylene glycol
Anhydrous citric acid
Peach flavour
Sodium benzoate
Sorbitol 70% solution
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.
After opening the bottle: 6 months

6.4 Special precautions for storage

Do not store above 25ºC.

6.5 Nature and contents of container

Amber glass bottle with measuring device. Each bottle contains 200 ml of syrup.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Laboratórios Basi – Indústria Farmacêutica, S.A.
Parque Industrial Manuel Lourenço Ferreira, Lotes 15 e 16
3450-232 Mortágua, Portugal
Tel.: +351 231 920 250

Fax: +351 231 921 055
E-mail: basi@basi.pt

8. MARKETING AUTHORISATION NUMBER(S)

Registration no.: 5704234 – 200 ml of syrup, 2 mg/ml, amber glass bottle

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 October 2014

10. DATE OF REVISION OF THE TEXT