SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

TOSSEQUE 0.8 mg/ml syrup

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of syrup contains 0.8 mg of bromhexine hydrochloride.

Excipients with known effect:
Liquid sorbitol (non-crystallising) (E420) – 571.4 mg/ml
Ethanol – 100 mg/ml
Red colouring agent (E122) – 0.03 mg/ml

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Syrup.

Clear, transparent, pink syrup with a characteristic flavour and smell.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

TOSSEQUE is indicated as a mucolytic adjuvant in the antibacterial treatment of respiratory infections involving bronchial hypersecretion.

4.2. Posology and method of administration

The recommended posology is as follows:

Adults and children older than 12 years: 10 ml 3 times a day;
Children aged 6 to 12 years: 5 ml 3 times a day;
Children aged 6 to 2 years: 2.5 ml 3 times a day;
Children younger than 2 years: 1.25 ml 3 times a day.

To facilitate the administration of the syrup the package contains a measuring spoon with markings compatible with the dosage indicated above.
1 full measuring spoon = 5 ml
To complete the 10ml dose, 2 full measuring spoons must be taken.

TOSSEQUE should only be administered to children younger than 2 years under medical supervision.

Use in renal insufficiency:
In patients with renal insufficiency, dose adjustment is not necessary.

Use in hepatic insufficiency:
In patients with hepatic insufficiency, dose adjustment is not necessary.

You should only take TOSSEQUE while symptoms persist, not exceeding seven consecutive days of therapy, unless expressly indicated by a doctor.

4.3. Contraindications

Hypersensitivity to bromhexine or to any of the excipients listed in section 6.1 and in patients with gastroduodenal ulcer.

4.4. Special warnings and precautions for use

TOSSEQUE should not be administered concomitantly with antitussives or secretion-drying medications. The use of mucolytics entails a decrease in mucus viscosity and its removal, both through the ciliary activity of the epithelium and the cough reflex; therefore, increased expectoration and cough are to be expected.

TOSSEQUE should be used with caution in individuals susceptible to gastroduodenal ulcers (for example, with a history of gastroduodenal ulcers), as its active substance, bromhexine, has the ability to destroy the gastric mucosal barrier. TOSSEQUE should also be taken with caution by patients with bronchial asthma.

There have been reports of severe skin reactions such as erythema multiforme, Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) and acute generalised exanthematous pustulosis (AGEP) associated with the administration of bromhexine. If symptoms or signs of a progressive skin rash (sometimes associated with blisters or mucosal lesions) are present, bromhexine treatment should be discontinued immediately and medical advice should be sought.

The elimination of bromhexine or its metabolites may be decreased in case of severe hepatic disease or renal insufficiency. Bromhexine should only be administered to these patients under medical supervision.

This medicinal product contains 12% (v/v) of ethanol (alcohol), i.e., up to 500 mg per dose (5ml ≈ 1 spoonful), equivalent to about 12 ml of beer or approximately 5 ml of wine per dose.

Harmful for those suffering from alcoholism.

To be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver disease, or epilepsy.

This medicine contains liquid sorbitol (non-crystallising) (E420). Patients with rare hereditary problems of fructose intolerance should not take this medicine.

This medicine contains red colouring agent (E122). May cause allergic reactions.

4.5. Interaction with other medicinal products and other forms of interaction

Do not associate antitussives or secretion-drying medications, since these have an opposite effect to that intended.

4.6. Fertility, pregnancy and lactation

Bromhexine crosses the placental barrier in small amounts. For this reason, although no adverse effects are described in pregnant women, TOSSEQUE should be administered with caution to pregnant women, particularly during the first trimester of pregnancy.

Since the excretion rate of bromhexine in breast milk is not adequately quantified, the administration of TOSSEQUE to nursing women should be avoided.

4.7. Effects on ability to drive and use machines

The effects of TOSSEQUE on ability to drive and use machines are null or negligible.

4.8. Undesirable effects

The frequency of adverse reactions is agreed as follows: Very common (≥ 1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000); Not known (cannot be estimated from the available data).

Immune system disorders
Rare: hypersensitivity reactions

Not known: anaphylactic reactions including anaphylactic shock, angioedema and pruritus

Skin and subcutaneous tissue disorders
Rare: rash, urticaria
Not known: Severe cutaneous adverse reactions (including erythema multiforme, Stevens-Johnson syndrome/toxic epidermal necrolysis and acute generalized exanthematous pustulosis).

Gastrointestinal disorders
Rare: nausea, vomiting, diarrhoea, epigastric pain.
Very rare: changes in AST and ALT values and GOT and GPT values.

Nervous system disorders:
Very rare: headache, dizziness.

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 INFARMED I.P. by the following contacts:

INFARMED, I.P.
Direção de Gestão do Risco de Medicamentos
Parque da Saúde de Lisboa, Av. Brasil 53
1749-004 Lisbon - PORTUGAL
Tél : +351 21 798 73 73
Product line : 800222444 (free)
Internet site: http://www.infarmed.pt/web/infarmed/submissaoram
E-mail : farmacovigilancia@infarmed.pt

4.9. Overdose

In case of overdose, TOSSEQUE may undesirably increase the volume of bronchial secretions.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: 5.2.2. Respiratory system. Antitussives and expectorants. Expectorants.
ATC code: R05CB02

Bromhexine hydrochloride is a benzylamine derivative (2-amino-3,5-dibromo-N-cyclohexyl-N-methylbenzylamine hydrochloride), as well as a synthetic derivative of vasicine, an active substance

extracted from the Indian plant *Adhatoda vasica*. Bromhexine acts by increasing the amount of secretions while reducing its viscosity.

Following oral administration, bromhexine increases the volume of expectorated sputum and reduces bronchial secretion viscosity.

Bromhexine acts through the depolymerisation of mucoprotein fibres and stimulates the activity of the ciliated epithelium, that is, this agent disrupts the disulphide bonds found in mucoproteins, thus fluidising bronchial secretions. Thus it has a secretolytic and secretomotor action on the bronchial tract, alleviating irritating cough and promoting expectoration. There are data supporting that bromhexine facilitates lysosomal activity.

5.2. Pharmacokinetic properties

Bromhexine hydrochloride is rapidly absorbed from the gastrointestinal tract, with concentration peaks reached about 1 hour after oral administration. Bromhexine is extensively metabolized in the liver (first-pass effect), with an oral bioavailability of approximately 20%.

Bromhexine is widely distributed to various organs and tissues. It binds extensively to plasma proteins (95-99%), crossing the blood-brain barrier and the placental barrier in small amounts.

Bromhexine is essentially excreted via the kidneys; approximately 85-90% of the administered dose is eliminated in the urine, mostly as metabolites. Ambroxol is an active metabolite of bromhexine. The elimination half-life is 6.5 hours.

5.3. Preclinical safety data

Bromhexine showed no teratogenic effects or effects on fertility. However, there were embryotoxic and developmental delays in rabbits at doses approximately 625 times (500 mg/kg) the maximum daily doses in humans.

Mutagenicity studies *in vitro and in vivo* (Ames test and the micronucleus in mice, respectively) were negative. In rats, bromhexine showed no carcinogenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Glycerol,
Liquid sorbitol (non-crystallising) (E420),
Monohydrate citric acid,
Dihydrate saccharin sodium (E954),

Povidone,
Red colouring agent (E122),
96% ethanol,
Benzoic acid (E210),
Gooseberry flavour,
Raspberry flavour,
Peppermint flavour and
Purified water.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

Do not store above 30ºC.

Keep the bottle inside the outer carton in order to protect from light.

6.5. Nature and contents of container

Amber glass bottles with child-proof cap.
Bottles containing 60 ml, 100 ml or 200 ml of syrup.
Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

No special requirements for disposal.

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

7. MARKETING AUTHORISATION HOLDER

MEDINFAR CONSUMER HEALTH – PRODUTOS FARMACÊUTICOS, LDA.
Rua Henrique Paiva Couceiro, n.º 27, Venda Nova
2700-451 Amadora
Portugal (EU)

8. MARKETING AUTHORISATION NUMBER(S)

< to be completed nationally >

9. DATE OF FIRST AUTHORISATION/RENEWAL OF MARKETING AUTHORISATION

< to be completed nationally >

10. DATE OF REVISION OF THE TEXT

07/2018