SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Bromhexine <TRADE NAME> <STRENGTH> Tablets

<REGARDING THE APPROVAL>

1. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablets contains <STRENGTH> of Bromhexine hydrochloride

For the full list of excipients, see section 6.1.

<REGARDING THE APPROVAL>

1. PHARMACEUTICAL FORM

Tablets <REGARDING THE APPROVAL>

1. CLINICAL PARTICULARS
   1. Therapeutic indications

For use as a mucolytic to break down mucus and help clear the chest in conditions accompanied by excessive mucus secretions, such as in the common cold, influenza, infections of the respiratory tract or in other conditions where excess mucus is produced.

* 1. Posology and method of administration

**Adults & Children 12 years and over**: One tablet (8 mg) three times a day when necessary. May be increased to two tablets (16 mg) three times a day for the first seven days.

**Children 6 - 11 years**: One tablet (8 mg) three times a day when necessary.

When infection is present, specific treatment with antibiotics could be indicated in addition to Bromhexine hydrochloride therapy.

Medical advice should be sought if symptoms do not improve rapidly.

**Method of administration**

For oral administration.

* 1. Contraindications

Not be used in patients known to be hypersensitive to bromhexine or any other excipients of the formulation.

* 1. Special warnings and precautions for use

Bromhexine should be used with caution in patients with severe liver disease and severe renal failure (refer to Section 5.2 Pharmacokinetic properties).

Use with caution in patients with gastric ulceration.

Patients should be advised to expect an increase in the flow of mucus secretions.

There have been very rare reports of severe skin lesions such as Stevens Johnson Syndrome

and toxic epidermal necrolysis (TEN) in temporal association with the administration of mucolytic substances such as bromhexine. Mostly, these could be explained by the patient’s underlying disease and/ or concomitant medication. In addition, during the early phase of a Stevens-Johnson syndrome or TEN a patient can first experience non-specific influenza-like prodromes like e.g fever, aching body, rhinitis, cough and sore throat. Misled by these non-specific influenza-like prodromes it is possible that a symptomatic treatment is started with a cough and cold medication. Therefore, if new skin or mucosal lesions occur, medical advice should be sought immediately and treatment with bromhexine should be discontinued as a precaution.

**Use in hepatic impairment**

Bromhexine should be used with caution in patients with severe liver disease. (refer to Section 5.2 Pharmacokinetic properties).

**Use in renal impairment**

Bromhexine should be used with caution in patients with severe renal failure (refer to Section 5.2 Pharmacokinetic properties)

**Use in the elderly**

There is no pharmacokinetic data available in the elderly or in patients with renal or liver insufficiency. (refer to Section 5.2 Pharmacokinetic properties)

**Effects on laboratory tests**

No data available

**Excipient information**

<REGARDING THE APPROVAL>

* 1. Interaction with other medicinal products and other forms of interaction

No clinically relevant unfavourable interactions with other medicines have been reported.

Following the administration of bromhexine, the antibiotic concentrations of amoxycillin, erythromycin and oxytetracycline in the sputum and bronchopulmonary secretions are increased.

Also, interaction studies with oral anticoagulants or digoxin were not performed. Bromhexine pharmacokinetics are not relevantly affected by co-administration of ampicillin or oxytetracycline. There was also no relevant interaction between bromhexine and erythromycin according to a historical comparison. The lack of any relevant interaction reports during the long-term marketing of the drug suggests no substantial interaction potential with these drugs.

* 1. Fertility, pregnancy and lactation

**Pregnancy**

Category A: Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed.

Bromhexine crosses the placental barrier. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development.

Clinical experience to date has shown no evidence of harmful effects on the foetus duringpregnancy. Nonetheless, the usual precautions regarding the use of drugs during pregnancyshould be observed. Especially during the first trimester, the use of Bromhexine is not recommended.

**Breast-feeding**

Bromhexine is excreted in breast milk. Although unfavourable effects on breastfed infants would not be expected, Bromhexine is not recommended for use in breastfeeding mothers.

**Fertility**

No data available.

* 1. Effects on ability to drive and use machines

When used as recommended and when there are no side effects, Bromhexine is not known to have any effect on the ability to drive or operate machinery.

* 1. Undesirable effects

**Immune system disorder**

Skin and subcutaneous tissue disorders and Respiratory, mediastinal and thoracic disorders.

**Anaphylactic reaction including anaphylactic shock**

Angioedema, bronchospasm, rash, urticaria, pruritus and other hypersensitivity.

**Gastro-intestinal disorders**

Nausea, vomiting, diarrhoea, upper abdominal pain and other mild gastrointestinal side effects.

**Nervous system disorders**

Headache, dizziness, sweating.

**Hepatic system disorders**

A transient rise in serum aminotransferase values.

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 Health Product Vigilance Center; HPVC.

* 1. Overdose

No specific overdose symptoms have been reported in man to date. Based on accidental overdose and/or medication error reports the observed symptoms are consistent with the known side effects of bromhexine at recommended doses and may need symptomatic treatment.

1. PHARMACOLOGICAL PROPERTIES
   1. Pharmacodynamic properties

**Mechanism of action**

Bromhexine hydrochloride is a mucolytic. It has been shown to enhance the transport of mucus by reducing its viscosity and by activating the ciliated epithelium (mucociliary clearance).

**Clinical trials**

Preclinical studies have shown that bromhexine increases the amount of thin watery bronchial secretion. Clinical studies show that bromhexine has a secretolytic and secretomotor effect in the bronchial tract area, which facilitates expectoration and eases cough.

Following the administration of bromhexine, the antibiotic concentrations of amoxycillin, erythromycin and oxytetracycline in the sputum and bronchopulmonary secretions are increased.

* 1. Pharmacokinetic properties

**Absorption**

Following oral administration, bromhexine shows dose linear pharmacokinetics in the dose range of 8-32 mg. It is rapidly and completely absorbed from the gastrointestinal tract. The bioavailability after oral administration is substantially reduced by an extensive first-pass effect in the range of 75-80%. The absolute bioavailability of bromhexine hydrochloride is about 22.2 ± 8.5 % and 26.8 ± 13.1 % for Bromhexine tablets and solution, respectively. Concomitant food intake leads to an increase of bromhexine plasma concentrations.

**Distribution**

After intravenous administration, bromhexine was rapidly and widely distributed throughout the body with a mean volume of distribution (Vss) of up to 1209 ± 206 L (19 L/kg). The distribution of bromhexine in lung tissue (bronchial and parenchymal) was investigated after oral administration of 32 mg and 64 mg bromhexine. Bromhexine lung tissue concentrations two hours post-dose were 1.5 to 3.2 times higher in bronchiolo-bronchial tissues and between 3.4 and 5.9 times higher in pulmonary parenchyma compared to plasma concentrations. Bromhexine crosses the blood-brain barrier and only a small amount crosses the placenta. Unchanged bromhexine is 95% bound to plasma proteins.

**Metabolism and elimination**

Bromhexine has a high extraction ratio drug after intravenous administration (clearance is 843-1073 mL/min, within the range of the hepatic blood flow) resulting in high inter- and intra-individual variability (CV > 30%). After administration of radiolabelled bromhexine, about 97.4 ± 1.9% of the dose was recovered in the urine, with less than 1% as the parent compound. Bromhexine plasma concentrations showed a multi-exponential decline. After administration of single oral doses between 8 and 32 mg, the terminal half-life of bromhexine ranged between 6.6 and 31.4 hours. The relevant half-life to predict the multiple dosepharmacokinetics is about 1 hour. No accumulation was observed after multiple dosing (accumulation factor 1.1).

Bromhexine is almost completely metabolised to a variety of hydroxylated metabolites and to dibromanthranilic acid. Ambroxol is a metabolite of bromhexine.

There is no pharmacokinetic data available in the elderly or in patients with renal or liver insufficiency. Extensive clinical experience did not give rise to relevant safety concerns in these populations. However, reduced clearance of bromhexine parent substance may be expected in the case of severe liver disease; in the case of severe renal insufficiency, accumulation of metabolites cannot be ruled out.

* 1. Preclinical safety data

No data available.

1. PHARMACEUTICAL PARTICULARS
   1. List of excipients

<REGARDING THE APPROVAL>

* 1. Incompatibilities

Not applicable.

* 1. Shelf life

<REGARDING THE APPROVAL>

* 1. Special precautions for storage

<REGARDING THE APPROVAL>

* 1. Nature and contents of container

<REGARDING THE APPROVAL>

* 1. Special precautions for disposal

<REGARDING THE APPROVAL>

1. MARKETING AUTHORISATION HOLDER

<REGARDING THE APPROVAL>

1. MARKETING AUTHORISATION NUMBER(S)

<REGARDING THE APPROVAL>

1. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<REGARDING THE APPROVAL>

1. DATE OF REVISION OF THE TEXT1

<REGARDING THE APPROVAL>