This leaflet format has been determined by the Ministry of Health and the content thereof has been checked and approved.”  Date of approval: 1/7/2014

**SOLVEX®**

**TABLETS. SOLUTION. ELIXIR**

**COMPOSITION**

**Solvex Tablets**
Each tablet contains:

**Active Ingredient**
Bromhexine hydrochloride  8 mg

**Other Ingredients**
Lactose, microcrystalline cellulose, starch, magnesium stearate, colloidal silicon dioxide, D&C yellow No.10.

*Lactose content: 85 mg per tablet.*

**Solvex Solution**
Each ml (20 drops) contains:

**Active Ingredient**
Bromhexine hydrochloride     2 mg

**Other Ingredients**
Methylparaben, tartaric acid, purified water.

**Solvex Elixir**
Each 5  ml contains:

**Active Ingredient**
Bromhexine hydrochloride     4 mg

**Other Ingredients**
Sorbitol solution 70%, glycerol, alcohol*, sodium carboxymethylcellulose, benzoic acid, aroma 502658T artificial, tartaric acid, purified water.

* Alcohol content: 150 mg/5 ml

**PHARMACOLOGICAL PROPERTIES**

**Pharmacodynamic properties**
Bromhexine is a synthetic derivative of the herbal active ingredient vasicine. Preclinically, it has been shown to increase the proportion of serous bronchial secretion. Bromhexine enhances mucus transport by reducing mucus viscosity and by activating the ciliated epithelium (mucociliary clearance).

In clinical studies, bromhexine showed a secretolytic and secretomotor effect in the bronchial tract area, which facilitates expectoration and eases cough.

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

For patient convenience, a new dosage form, namely a specially formulated palatable elixir has been added to Solvex Tablets and Solvex Solution.
Pharmacokinetic properties
Absorption
Bromhexine is rapidly absorbed from the gastrointestinal tract; peak plasma levels are reached within 30 minutes to one hour. Plasma protein binding is above 90% with a high rate of tissue penetration, especially in the bronchopulmonary tissue. Bromhexine is excreted in the urine (85%), mainly as a metabolite.

The first pass metabolism amounts to about 75-80%. Concomitant food 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 into lung tissue (bronchial and parenchymal) was investigated after oral administration of 32 mg and 64 mg bromhexine. Lung tissue concentrations two hours post dose 1.5 -4.5 times higher in bronchiole-bronchial tissues and between 2.4 and 5.9 times higher in pulmonary parenchyma compared to plasma concentrations.

Unchanged bromhexine is bound to plasma proteins by 95 % (non-restrictive binding).

Metabolism
Bromhexine is almost completely metabolised to a variety of hydroxylated metabolites and to dibromanthranilic acid. All metabolites and bromhexine itself are conjugated most probably in form of N-glucuronides and O-glucuronides. There are no substantial hints for a change of the metabolic pattern by a sulphonamide or oxytetracyclin. There is insufficient pharmacokinetic data to evaluate a possible drug-drug interaction between bromhexine and erythromycin.

Elimination
Bromhexine is a high extraction ratio drug after I.V. administration in the range of the hepatic blood flow, 843-1073 ml/min resulting in high inter- and intraindividual variability (CV > 30 %) After administration of radiolabelled bromhexine about 97.4 ± 1.9 % of the dose were recovered as radioactivity in urine, with less than 1% as parent compound.

Bromhexine plasma concentrations showed a multiexponential decline. After administration of single oral doses between 8 and 32 mg, the terminal elimination half-life ranged between 6.6 and 31.4 hours. The relevant half-life to predict the multiple dose pharmacokinetics is about 1 hour, thus no accumulation was seen after multiple dosing (accumulation factor 1.1).

General
Bromhexine shows dose proportional pharmacokinetics in the range of 8-32 mg following oral administration. There are no data for bromhexine pharmacokinetics in the elderly or in patients with renal or liver insufficiency.

Bromhexine pharmacokinetics are not relevantly affected by co-administration of ampicillin or oxytetracycline.

Interaction studies with oral anticoagulants or digoxin were not performed.

Indications
Mucolitic expectorant in conditions associated with the retention of viscid mucoid secretion in the respiratory tract e.g.: bronchitis, asthma and sinusitis.
Contraindications
Known hypersensitivity to the preparation.

Warnings
There have been very rare reports of severe skin lesions such as Stevens-Johnson syndrome and Lyell’s syndrome/toxic epidermal necrolysis (TEN) in temporal association with the administration of mucolytic substances such as bromhexine. Mostly these could be explained by the severity of the underlying disease 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 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. If new skin or mucosal lesions occur, medical advice should be sought immediately and treatment with bromhexine discontinued as a precaution.

Fertility
No studies on the effect on human fertility have been conducted with bromhexine. Based on available pre-clinical experience there are no indications for possible effects of the use of bromhexine on fertility.

Use in Pregnancy
Safety of use in pregnancy has not been established. 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 during pregnancy. Nonetheless, the usual precautions regarding the use of drugs during pregnancy, should be observed. Especially during the first trimester, the use of this preparation is not recommended.

Use in Breastfeeding
Bromhexine is excreted in breast milk. Although unfavourable effects on breastfed infants would not be expected, this preparation is not recommended for use in nursing mothers.

Use in Pediatrics
Solvex is not recommended for administration to infants under 1 year of age.

Adverse Reactions
Summary of the safety profile
Gastrointestinal adverse effects may occur occasionally with bromhexine and a transient rise in serum aminotransferase values has been reported. Other reported adverse effects include headache, dizziness, sweating, and skin rashes. Inhalation of bromhexine has occasionally produced bronchospasm in susceptible subjects.

List of adverse reactions
The frequencies of adverse events are ranked according to the following: 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 (cannot be estimated from the available data).

Immune system disorders
Rare: Hypersensitivity
Not known: Anaphylactic reaction, anaphylactic shock
Nervous system disorders
Not known: Headache, dizziness

Respiratory, thoracic and mediastinal disorders
Not known: Bronchospasm

Gastrointestinal disorders
Uncommon: Abdominal pain upper, nausea, vomiting, diarrhoea
Not known: Dyspepsia

Skin and subcutaneous tissue disorders
Rare: Rash
Not known: Angioedema, urticaria, pruritus, hyperhidrosis

Investigations
Not known: Hepatic enzyme increased

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.

Precautions
Caution must be taken in patients with a history of, or existing peptic ulceration, since bromhexine may disrupt the gastric mucosal barrier.

Because of the alcohol content of Solvex Elixir, this medicine may cause drowsiness in children. Children should therefore be cautioned against engaging in activities such as bicycle riding or playing near traffic.

Solvex solution contains methylparaben (methyl-parahydroxybenzoate) which may cause allergic reactions (possibly delayed).

Solvex Elixir contains 2 g of sorbitol in each 5 ml. It has been reported that the maximum allowed daily intake of sorbitol for diabetics is 25 g. It should be noted that the amount of sorbitol included in the adult dosage of Solvex Elixir may extend beyond the allowed daily consumption of sorbitol for diabetics.

Solvex tablets contain lactose (85 mg per tablet). Patients with rare hereditary problems of galactose intolerance e.g. galactosaemia should not take this medicine.

Interaction with other medicinal products and other forms of interaction
No clinically relevant unfavourable interactions with other medications have been reported.

Diagnostic Interference:
In very few patients, a transitory rise in serum transaminase levels may be seen during treatment with bromhexine. With continued administration of the drug, transaminases return to pre-treatment levels, even in those patients with pre-existing impairment of hepatic function.

Dosage and Administration

Note: Use the measuring cups supplied for Solvex Solution and Elixir.
**Oral**

Tablets
- Adults and children over 12 years: 8 mg (1 tablet) 3 times daily
- Children 6 - 12 years: 4 mg (1/2 tablet) 3 times daily
- Children 2 - 6 years: 4 mg (1/2 tablet) 2 times daily

Elixir:
- Adults and children over 12 years: 10 ml 3 times daily
- Children 6 - 12 years: 5 ml 3 times daily
- Children 2 - 6 years: 2.5 ml 3 times daily
- Children under 2 years: 1.25 ml 3 times daily

Solution
- Adults and children over 12 years: 4 ml 3 times daily
- Children 6 - 12 years: 2 ml 3 times daily
- Children 2 - 6 years: 20 drops 3 times daily
- Children under 2 years: 13 drops 3 times daily

**Inhalation**
Solvex solution may be used for inhalation using conventional inhalers.
- Adults: 4 ml 2 times daily
- Children over 12 years: 2 ml 2 times daily
- Children 6 - 12 years: 1 ml 2 times daily
- Children 2 - 6 years: 13 drops 2 times daily
- Children under 2 years: 7 drops 2 times daily

**Overdosage**
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 the product at recommended doses and may need symptomatic treatment.

**Storage**
Solvex tablets: Store in a dry and dark place below 25°C
Solvex Solution: Store in a dark place below 25°C. Solvex solution may be used up to 1 year following first opening of the bottle, but no later than the expiry date.
Solvex Elixir: Store in a dark place below 25°C.

**Registration Numbers**
- Solvex Tablets: 063 72 22688 01.
- Solvex Solution: 027 59 21677 00.
- Solvex Elixir: 057 35 27023 00.

**Presentation**
- **Solvex Tablets:** 20 tablets.
- **Solvex Solution:** Dropper bottles of 50 ml, with measuring cup.
- **Solvex Elixir:** Bottles of 100 ml, with measuring cup.

**Manufacturer**
TEVA PHARMACEUTICAL INDUSTRIES LTD
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