SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Bisolvon 4 mg/5 ml Oral Solution

2. Qualitative and quantitative composition

Each 5 ml contains bromhexine hydrochloride 4 mg.

Excipients: contains maltitol liquid

For a full list of excipients, see section 6.1

3. Pharmaceutical form

Oral solution

A clear to almost clear, colourless to almost colourless solution with a fruity aromatic odour.

4. Clinical particulars

4.1 Therapeutic Indications

As a mucolytic in the management of viscid mucoid secretions associated with bronchitis, bronchiectasis, sinusitis.

4.2 Posology and method of administration

Oral.

Adults and children over 12 years:

Recommended total daily dose	Recommended maximum daily dose
10 ml (8 mg) three times daily	15 ml (12 mg) four times daily

The recommended maximum daily dose which may be needed at the commencement of treatment should not be exceeded.

Children over 5 to ≤ 12 years: Recommended total daily dose 5 ml (4 mg) four times daily.

Children 2 to ≤ 5 years: Recommended total daily dose 5 ml (4 mg) twice daily.

The measuring cup provided should be used for dosing.

BISOLVON can be taken with or without food (see section 5.2).

Additional information on specific populations
BISOLVON Oral Solution is sugar free and therefore suitable for diabetes patients.

4.3 Contraindications

Bisolvon Oral Solution is contraindicated in patients known to be hypersensitive to bromhexine or other excipients of the formulation.

4.4 Special warnings and precautions for use

Bromhexine should be used with caution in patients with a history of, or existing, peptic ulceration.

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 hydrochloride. If symptoms or signs of a progressive skin rash (sometimes associated with blisters or mucosal lesions) are present, bromhexine hydrochloride treatment should be discontinued immediately and medical advice should be sought.

As the product contains maltitol liquid, patients with rare hereditary problems of fructose intolerance should not take this medicine.

This product may have a mild laxative effect.

Each 5 ml dose supplies up to 2.5 g of maltitol liquid which has a calorific value of 5.75 Kcal.

4.5 Interaction with other medicinal products and other forms of interaction

No clinically relevant unfavourable interactions with other medications, such as ampicillin, amoxicillin, oxytetracycline or erythromycin, have been reported (see section 5.1).

4.6 Fertility, pregnancy and lactation

Pregnancy
There are limited data from the use of bromhexine in pregnant women.
Pre-clinical studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of BISOLVON during pregnancy.

Lactation
It is unknown whether bromhexine/metabolites are excreted in human milk.
Available pharmacodynamic/toxicological data in pre-clinical studies have shown excretion of bromhexine in breast milk. A risk to the breastfed infant cannot be excluded.
BISOLVON should not be used during breast-feeding.

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

4.7 Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed with BISOLVON.

4.8 Undesirable effects

The following side effects have been reported based on clinical trials involving 3,992 patients

Frequencies

Very common ≥1/10
Common ≥ 1/100 < 1/10
Uncommon ≥ 1/1,000 < 1/100
Rare ≥ 1/10,000 < 1/1,000
Very rare < 1/10,000
Not known cannot be estimated from the available data

Immune system disorders	
Hypersensitivity reactions	Rare
Anaphylactic reactions including anaphylactic shock*	Not known
Respiratory, thoracic and mediastinal disorders	
Bronchospasm*	Not known
Gastro-intestinal disorders	
Abdominal pain upper	Uncommon
Nausea	Uncommon
Vomiting	Uncommon
Diarrhoea	Uncommon
Skin and subcutaneous tissue disorders	
Rash	Rare
Urticaria*	Rare
Pruritus*	Not known
Angioedema*	Not known
Severe cutaneous adverse reactions (including erythema multiforme, Stevens-Johnson syndrome/toxic epidermal necrolysis and acute generalized exanthematous pustulosis)	Not known

**This adverse reaction has been observed in post-marketing experience. With 95 % certainty, the frequency category is not greater than rare (3/3,992), but might be lower. A precise frequency estimation is not possible as the adverse drug reaction did not occur in a clinical trial database of 3,992 patients.*

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product isimportant. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via: ADR Reporting Website: www.medicinesauthority.gov.mt/adrportal.

4.9 Overdose

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

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Expectorants, excl. combinations with cough suppressants

ATC-Code: R05CB02

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.

Drug/ drug interactions in Pharmacodynamics and Pharmacokinetics
Following the administration of bromhexine antibiotic concentrations (amoxycillin, erythromycin, oxytetracycline) in the sputum and bronchopulmonary secretions are increased.

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

5.2 Pharmacokinetic properties

Absorption
Bromhexine is rapidly and completely absorbed from the gastrointestinal tract.

After oral administration solid and liquid formulations show similar bioavailability. The absolute bioavailability of bromhexine hydrochloride was about 22.2 ± 8.5 % and 26.8 ± 13.1 % for BISOLVON® tablets and solution, respectively. 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 (V_{ss}) 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 - 3.2 times higher in bronchiolo-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).

Linearity/Non-linearity

Bromhexine shows dose proportional pharmacokinetics in the range of 8-32 mg following oral administration.

Special populations
There are no data for bromhexine pharmacokinetics in the elderly or in patients with renal or liver insufficiency.

5.3 Preclinical safety data

No details on schedule.

6. Pharmaceutical particulars

6.1 List of excipients

Maltitol liquid (E965)
Sucralose (E955)
Benzoic acid (E210)
Cherry aroma 96323-33
Chocolate aroma 96534-33
Levomenthol
Water, purified

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened: 3 years.

In-use: Use within 12 months of opening bottle.

6.4 Special precautions for storage

Store in the original container.

6.5 Nature and contents of container

Bisolvon Oral Solution is available in amber type III glass bottles with tamper-evident polyethylene caps with low density polyethylene liners. The registered pack sizes are 100 ml, 200 ml and 250 ml.

Not all pack sizes may be marketed.

A polypropylene measuring dish is provided.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7. Marketing authorisation holder

Opella Healthcare France SAS

157 avenue Charles de Gaulle
92200 Neuilly-sur-Seine
(France)

8. Marketing authorisation number

MA1470/00101

9. Date of first authorisation/renewal of the authorisation

27th November 2006 / 1st December 2009

10. Date of revision of the text

July 2023