Applicant/HCR	sanofi-aventis south africa (pty) ltd
Product name, strength & dosage form	Bisolvon 0,2 % Solution, 10 mg per 5 mL solution
Variation classification & codes	Compliant response to CCR, dated 17/03/2022
Date of this submission	21 March 2022

Approved Professional Information for BISOLVON® 0,2 % solution (Clean Copy)

SCHEDULING STATUS

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1. NAME OF THE MEDICINE

BISOLVON® 0,2 % solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The solution contains bromhexine hydrochloride 10 mg per 5 mL.

Preservative: Methyl parahydroxybenzoate 0,1 % *m/v*.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution.

A clear, colourless liquid with a slightly bitter taste.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic relief of cough, associated with non-purulent excessive sputum production.

4.2 Posology and method of administration

Posology

Oral:

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Adults and children over 10 years: 5 - 10 mL three times a day.

Children under 10 years: 2,5 - 5 mL three times a day.

Inhalation from a respirator:

Adults: 4 mL twice a day.

Children over 12 years: 2 mL twice a day.

Children over 6 to ≤ 12 years: 1 mL twice a day.

Children 2 to ≤ 6 years: 10 drops twice a day.

Children under 2 years: 5 drops twice a day.

Warming the solution prevents the possible occurrence of an initial irritating cough. If the preparation is used in the presence of bronchospasm, a bronchodilator should first be administered.

The solution may be diluted 1:1 with physiological saline solution. In order to avoid precipitation the solution should be inhaled immediately after mixing.

Note: Patients being treated with BISOLVON 0,2 % solution should be notified of an expected increase in the flow of secretions.

The duration of treatment should be determined on an individual basis depending on the response.

BISOLVON 0,2% solution should not be taken for more than 5 days without medical advice.

Special populations

Paediatric population:

See the paediatric dosage stated above.

BISOLVON 0,2 % solution is not recommended for children 2 years or less (see section 4.4).

The elderly, and patients with renal and hepatic impairment.

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

4.3 Contraindications

Hypersensitivity to bromhexine or the excipients of the formulation listed in section 6.1.

4.4 Special warnings and precautions for use

There have been reports of severe skin lesions such as Stevens Johnson syndrome and Lyell's syndrome in temporal association with the administration of secretolytic substances such as bromhexine, as contained in BISOLVON 0,2 % solution. Mostly these could be explained by the severity of the underlying disease or concomitant medication. If new skin or mucosal lesions occur, medical advice should be sought immediately and treatment with BISOLVON 0,2 % solution discontinued as a precaution.

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

Care is advisable in asthmatic patients.

Concomitant administration with cough suppressants such as opioids analgesics is not recommended.

In patients with impaired renal function or severe liver disease BISOLVON 0,2 % solution must be used with particular caution (i.e. at reduced doses or longer dosing intervals). See section 4.2.

In patients with severe renal impairment, accumulation of the metabolites of bromhexine which are formed in the liver can be expected to occur. See section 4.2.

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Occasional monitoring of liver function is advisable, especially on longer-term use.

BISOLVON 0,2 % solution must not be given to children under 2 years except under medical supervision.

BISOLVON 0,2 % solution contains 5 mg of the excipient methyl parahydroxybenzoate in each 5 mL of oral solution, which may cause allergic reactions (possibly delayed).

4.5 Interaction with other medicines and other forms of interaction

Concomitant administration of BISOLVON 0,2 % solution and cough suppressants may lead to the development of a dangerous accumulation of secretions owing to attenuation of the cough reflex and should be undertaken only after very careful risk-benefit assessment.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited data from the use of bromhexine in pregnant women.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

As a precaution, the use of bromhexine should be avoided during pregnancy.

Breastfeeding

Bromhexine has been shown to be excreted in the milk in animal studies. Use during lactation is not recommended.

Fertility

No studies on the effect of BISOLVON 0,2 % solution on fertility have been performed.

There is no evidence from the available preclinical studies to suggest that bromhexine has any effect on fertility.

4.7 Effects on ability to drive and use machines

BISOLVON 0,2 % solution may cause dizziness. Patients experiencing dizziness should avoid driving and use of machines.

4.8 Undesirable effects

The frequency of undesirable effects is defined using the following convention:

Very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1000, < 1/100); rare (≥ 1/10 000, < 1/1000); very rare (< 1/10 000).

Not known (Frequency cannot be estimated from the available data).

System organ class	**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)**	**Not known**
Immune system disorders					
Hypersensitivity reactions				X	
Anaphylactic reactions including shock, angioedema and pruritis					X
Nervous system disorders					
Headache				X	
Dizziness				X	
Sweating				X	

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Respiratory, thoracic and mediastinal disorders					
Bronchospasm				X	
Dyspnoea (as a symptom of a hypersensitive reaction)					X
Gastrointestinal disorders					
Nausea		X			
Abdominal pain (especially upper abdominal pain)		X			
Vomiting		X			
Diarrhoea		X			
Skin and subcutaneous tissue disorders					
Rash				X	
Urticaria				X	
Severe cutaneous adverse reactions including erythema multiforme, Steven-Johnson syndrome/ toxic epidermal necrolysis and acute exanthematous pustulosis					X
General disorders and administration site conditions					

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Fever			X		

Methyl parahydroxybenzoate may cause hypersensitivity reactions (possibly delayed).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of BISOLVON 0,2 % solution is important. It allows continued monitoring of the benefit/risk balance of BISOLVON 0,2 % solution. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

- https://www.sahpra.org.za/Publications/Index/8, or to the
- Pharmacovigilance Unit at Sanofi at za.drugsafety@sanofi.com (email) or 011 256 3700 (tel).

4.9 Overdose

Symptoms of overdose

No hazardous symptoms of overdose are known to have occurred in man to date. The symptoms which have been observed on accidental or deliberate overdose to date are identical with the known undesirable effects and may require symptomatic treatment.

Management of overdose

Following massive overdose, cardiovascular monitoring and, where appropriate, symptomatic treatment are indicated. In view of the low toxicity of bromhexine, more intensive measures to reduce absorption or accelerate elimination are generally not required. In addition, the pharmacokinetic profile of bromhexine is characterised by a high distribution volume, slow redistribution processes and a high level of protein binding and elimination is therefore unlikely to be significantly affected by dialysis or forced diuresis.

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In children aged 2 years and above, symptoms are likely to be relatively mild even after ingestion of quite large amounts of bromhexine hydrochloride and decontamination is therefore not required where the amount ingested is less than 80 mg (e.g. 40 mL BISOLVON 0,2 % solution). The corresponding threshold in children aged under 2 years is 60 mg (6 mg/kg).

In one published case review, it was reported that vomiting occurred in 4 out of 25 cases where excessive doses of bromhexine had been taken and that 3 young children had experienced impaired consciousness, ataxia, diplopia, mild metabolic acidosis and tachypnoea. Young children remained symptom-free, even, without decontamination after ingesting up to 40 mg bromhexine.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Bromhexine hydrochloride belongs to the medicine class A 10.1
Antitussives and expectorants.

Bromhexine is a synthetic derivative of the herbal active ingredient vasicine. It has secretolytic and secretomotor effect in the respiratory tract and has been shown in clinical studies to ease cough and facilitate expectoration. Bromhexine reduces mucus viscosity and activates the ciliated epithelium (mucociliary clearance).

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

5.2 Pharmacokinetic properties

Bromhexine is well absorbed from the gastrointestinal tract with peak plasma concentrations after 1 hour. Bromhexine undergoes extensive first-pass metabolism (75 - 80 %) and has an average

bioavailability of 26,8 %. Bromhexine is widely distributed throughout the body, with a mean volume of distribution of 1 209 litres. It is 95 % bound to plasma proteins. It crosses the blood-brain barrier and small amounts cross the placenta. Concomitant intake of food leads to increase in plasma bromhexine concentrations.

Bromhexine is almost completely metabolised to a variety of hydroxylated metabolites and dibromoanthranic acid. Bromhexine and its metabolites undergo conjugation, principally to *N*-glucuronides and *O*-glucuronides. It is primarily excreted in urine and its terminal half-life after a single oral dose ranges between 6,6 and 31,4 hours.

5.3 Preclinical safety data

Bromhexine was not teratogenic or embryotoxic at doses of up to 300 mg/kg in rats and 200 mg/kg in rabbits. Fertility was not impaired at doses up to 300 mg/kg. Peri- and postnatal development was not impaired.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Purified water

Tartaric acid

Methyl parahydroxybenzoate.

6.2 Incompatibilities

None known.

6.3 Shelf life

36 months.

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6.4 Special precautions for storage

Store at or below 25 °C.

6.5 Nature and contents of container

50 mL solution in amber-coloured glass bottles with tamper-evident closure.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

sanofi-aventis south africa (pty) ltd

2 Bond Street

Midrand 1685

South Africa

8. REGISTRATION NUMBER

G642 (Act 101/1965)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Old Medicine.

10. DATE OF REVISION OF THE TEXT

17/03/2022

BOTSWANA Reg. No. B9304975	S3
NAMIBIA Reg. No. 14/10.1/0198	NS1

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