PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands

Bisolvon oral solution in sachet, 8 mg
Boehringer Ingelheim B.V., the Netherlands

bromhexine hydrochloride

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB. It reflects the scientific conclusion reached by the MEB at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.

This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB’s knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

Registration number in the Netherlands: RVG 111840

11 November 2013

Pharmacotherapeutic group: mucolytics
ATC code: R05CB02
Route of administration: oral
Therapeutic indication: secretolytic therapy in acute and chronic bronchopulmonary diseases associated with abnormal mucus secretion and impaired mucus transport

Prescription status: non prescription
Date of authorisation in NL: 12 March 2013
Application type/legal basis: Directive 2001/83/EC, Article 8(3)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SmPC), package leaflet and labelling.
I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board of the Netherlands (MEB) has granted a marketing authorisation for Bisolvon oral solution in sachet, 8 mg from Boehringer Ingelheim B.V. The date of authorisation was on 12 March 2013 in the Netherlands.

The product is indicated for secretolytic therapy in acute and chronic bronchopulmonary diseases associated with abnormal mucus secretion and impaired mucus transport.

A comprehensive description of the indications and posology is given in the SmPC.

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.

This national procedure concerns a line extension to the registered product Bisolvon oral solution 8 mg/5 ml (NL License RVG 09554) which has been registered since 1982. The differences with the original product are related to the composition (excipients) and packaging (single-dose sachets versus multi-dose 125 mL brown glass bottles).

The marketing authorisation is granted based on article 8(3) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the previous Bisolvon authorisations. This information is not fully available in the public domain. Authorisations for line extensions are therefore linked to the ‘original’ authorised medicinal product. Reference is made to the non-clinical and clinical studies performed with Bisolvon 8 mg/5 ml oral solution.

Bisolvon oral solution in sachet is an aqueous oral solution at time of administration and contains a drug substance in the same concentration as an oral solution currently approved as the currently approved Bisolvon formulation. In this case a bioequivalence study is not required, provided the excipients do not affect gastrointestinal transit, absorption or in vivo stability of the drug substance. The MAH applied for a biowaiver. Assessment thereof is discussed in section II.3 ‘Clinical aspects’.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a line extension.
II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is bromhexine hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is very slightly soluble in water, slightly soluble in alcohol and in methylene chloride. The active substance shows polymorphism.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The MAH applies the Ph.Eur monograph and the additional CEP requirements. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three batches.

Stability of drug substance
The active substance is stable for 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

* Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.

Medicinal Product

Composition
Bisolvon oral solution in sachet contains as active substance 8 mg bromhexine hydrochloride. It is a clear to almost clear, colourless to almost colourless solution with a fruity, aromatic odour and pH 2.5 to 4.0.

The oral solution is packed in 5 ml three-layer sachets (polyester/aluminium/polyacrylonitil).

The excipients are: sucralose (E955), hydroxyethylcellulose, benzoic acid (E210), cherry flavour, chocolate flavour, levomenthol, purified water.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. It concerns a line extension of Bisolvon oral solution 8 mg/5 ml. The objective was the development of a bromhexine hydrochloride oral solution packaged in single-dose stick packs. This kind of dosage form offers flexibility and convenience to the patient, as the medication can be taken on the go without the need for water or measuring devices.
Both formulations, the reference preparation and the test product bromhexine hydrochloride stick pack formulation are liquid oral dosage forms containing 8 mg bromhexine per 5 ml. The composition of the proposed drug product (sachets) differs with the already registered product on the following points:
- presence of more sucralose
- presence of hydroxyethylcellulose
- presence of less benzoic acid
- absence of maltitol

According to the note for guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), if the drug product is an aqueous oral solution at time of administration and contains a drug substance in the same concentration as an oral solution currently approved as a medicinal product, no bioequivalence study is required, provided the excipients contained in it do not affect gastrointestinal transit, absorption or in vivo stability of the drug substance. The drug product Bisolvon 8 mg fully complies with these requirements.

The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The product is manufactured by means of a 9 step process including introduction of active substance, sweeteners and flavourings. By mixing and filtering of the solution the final product is prepared.

The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three industrial-scale batches. The product is manufactured using conventional manufacturing techniques.

Control of excipients
All excipients comply with their specifications of the Ph.Eur. monographs. For chocolate flavour and cherry flavour specifications are according to the company standards. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, odour, clarity and colour of solution, relative density, pH, filling volume, uniformity of dosage units, identification, degradation products, assay, microbial contamination, preservative efficacy test and assessment of packaging materials.

Release and end of shelf-life specification are identical except for colour of solution and degradation products.

The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three production-scale batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for three full-scale batches stored at 25°C/60% RH (9 months) and 30°C/75% RH (9 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in 5 ml sachets of PET/Al/PAN. Results stayed within limits. Photostability studies have not been performed with the product, as both primary packaging materials employed consist of an aluminium layer in the middle of each compound film, which is impenetrable to light.

A shelf-life of 18 months stored in the stick pack 5 ml sachets was granted based on the provided data; the product does not require any special storage conditions. After finalisation of the national registration procedure, a IB variation was approved through which the shelf life was extended to 30 months.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.2  Non-clinical aspects

This product is a line extension to Bisolvon oral solution 8 mg/5 ml, which is available on the European market. No new preclinical data have been submitted. Therefore the application has not undergone additional preclinical assessment, which is acceptable for this type of application.
A non-clinical overview of the studies performed with regard to the pharmacology, pharmacokinetics and toxicology has been provided, which is based on non-clinical studies and supported by up-to-date and adequate scientific literature.

Environmental risk assessment
The product is intended as a substitute for other bromhexine hydrochloride containing products on the market. The approval of this product will not result in an increase in the total quantity of bromhexine hydrochloride released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects
Bromhexine hydrochloride is a well-known active substance with established efficacy and tolerability. Various oral immediate-release dosage forms have already been introduced into the market as solid (tablets) or liquid (solution, syrup) preparations. Bromhexine is used as API (active pharmaceutical ingredient) in these products together with a variety of excipients. All liquid forms are based on purified water.

A biowaiver for a comparative bioavailability study is requested. The formulation “Bisolvon oral solution in sachet” is quantitatively identical to the marketed syrup formulation with respect to content of active substance (8 mg/5 ml).

According to the note for guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98/REV1.), if the drug product is an aqueous oral solution at time of administration and contains a drug substance in the same concentration as an oral solution currently approved as a medicinal product, no bioequivalence study is required, provided the excipients contained in it do not affect gastrointestinal transit, absorption or in vivo stability of the drug substance.

In the Bisolvon in sachet formulation, the sweetener maltitol is replaced by sucralose. In contrast to maltitol, sucralose does not affect the osmolarity of the solution. Bisolvon sachets have a lower osmolarity compared to Bisolvon oral solution 8 mg/5 ml. Effects of maltitol on gastrointestinal transit due to osmotic behavior were reported to occur at doses > 0.3 g/kg body weight. The maximal dose of bromhexine contains 5 g maltitol. It is therefore agreed that it is unlikely that the different formulations will affect the pharmacokinetic properties of bromhexine in adults and children > 10 years of age.

Overall, the biowaiver for Bisolvon oral solution in sachet 8 mg can be granted. Despite the differences in composition, the product may be considered bioequivalent to the authorized product Bisolvon oral solution 8mg/5 ml.

Risk management plan
Bromhexine hydrochloride has been on the market for several decades. The safety profile of bromhexine hydrochloride can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SmPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Based on the considerable clinical experience, the well-established safety profile and the extensive knowledge through continuous post-marketing surveillance of Bisolvon® products the compilation of a risk management plan is not considered to be necessary.

Product information
SmPC
The content of the SmPC approved during the national procedure is in accordance with that accepted for the original product Bisolvon oral solution 8 mg/5 ml.

Readability test
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test with one participant, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results obtained fulfil the requirements of the current EU Readability Guideline and suggest that, following the two testing rounds, the package leaflet of Bisolvon oral solution in sachet, 8 mg was written in such a way that most potential users (patients) are able to trace, comprehend and apply the information given in leaflet. The readability test has been sufficiently performed.
III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Bisolvon oral solution in sachet 8 mg has a proven chemical-pharmaceutical quality and is a legitimate line extension to Bisolvon oral solution 8 mg/5 ml. Bisolvon is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both products are aqueous oral solutions at time of administration, containing bromhexine hydrochloride in the same concentration, bioequivalence studies were not required. All conditions for granting a biowaiver are fulfilled.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SmPC, package leaflet and labelling are in the agreed templates and are in agreement with other approved Bisolvon products.

The Board followed the advice of the assessors. The MEB, on the basis of the data submitted, has therefore granted a marketing authorisation. Bisolvon oral solution in sachet 8 mg was authorised in the Netherlands on 12 March 2013.

There were no post-approval commitments made during the procedure.
List of abbreviations

ASMF   Active Substance Master File
ATC    Anatomical Therapeutic Chemical classification
AUC    Area Under the Curve
BP     British Pharmacopoeia
CEP    Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP   Committee for Medicinal Products for Human Use
CI     Confidence Interval
Cmax   Maximum plasma concentration
CMD(h) Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV     Coefficient of Variation
EDMF   European Drug Master File
EDQM   European Directorate for the Quality of Medicines
EU     European Union
GCP    Good Clinical Practice
GLP    Good Laboratory Practice
GMP    Good Manufacturing Practice
ICH    International Conference of Harmonisation
MAH    Marketing Authorisation Holder
MEB    Medicines Evaluation Board in the Netherlands
OTC    Over The Counter (to be supplied without prescription)
PAR    Public Assessment Report
Ph.Eur. European Pharmacopoeia
PIL    Package Leaflet
PSUR   Periodic Safety Update Report
SD     Standard Deviation
SPC    Summary of Product Characteristics
t½     Half-life
tmax   Time for maximum concentration
TSE    Transmissible Spongiform Encephalopathy
USP    Pharmacopoeia in the United States
### STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

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<th>Scope</th>
<th>Type of modification</th>
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<th>Date of end of the procedure</th>
<th>Approval/ non approval</th>
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<td>17-4-2013</td>
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<td>6-5-2013</td>
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