CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Water voor injecties B. Braun, solvent for parenteral use 100% m/v B. Braun Melsungen AG, Germany

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 33585

1 September 2010

Pharmacotherapeutic group:	solvents and diluting agents, incl. irrigating solutions
ATC code:	V07AB
Route of administration:	parenteral
Therapeutic indication:	dissolvent and diluent for injectable medicines.
Prescription status:	prescription only
Date of authorisation in NL:	12 April 2007
Application type/legal basis:	Directive 2001/83/EC, Article 10a

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

I INTRODUCTION

Based on the review of the quality and safety data, the Medicines Evaluation Board of the Netherlands (MEB) has granted a marketing authorisation for Water voor voor injecties B. Braun, solvent for parenteral use 100% m/v from B. Braun Melsungen AG. The date of authorisation was on 12 April 2007 in the Netherlands.

Water for injections is used as a dissolvent and diluent for injectable medicines.

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

Water for injections being only the vehicle for the administration of the added medicinal product, the pharmacodynamics will depend on the nature of the drug added.

This is a national application in accordance with article 10a of Directive 2001/83/EC; a so called 'bibliographical application'.

This application concerns a bibliographical application based on well-established medicinal use of water for injections. This type of application does not require submission of the results of pre-clinical tests or clinical trials if the applicant can demonstrate that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least 10 years, with recognised efficacy and an acceptable level of safety. ''Medicinal use'' does not exclusively mean ''use as an authorised medicinal product'', so that the proof of medicinal use may be submitted even in the absence of a marketing authorisation. Well-established use refers to the use for a specific therapeutic use. For this kind of application, a detailed description of the strategy used for the search of published literature and the justification for inclusion of the references in the application has to be provided. The documentation submitted by the applicant should cover all aspects of the assessment and must include a review of the relevant literature, taking into account pre- and post-marketing studies and published scientific literature concerning experience in the form of epidemiological studies and in particular of comparative epidemiological studies.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

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 well-established use application.

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
As the product does not involve an active substance, all information on the quality of the water for injections has been laid down the 'medicinal product' section. This is acceptable.

Medicinal Product

Composition
Water voor injecties B. Braun contains 100% m/v water for injections. No excipients are used.

The product is available in small and larger containers (10 to 1000 ml).
Containers for infusion:
- Glass bottles of colourless glass, sealed with elastomeric closures which are retained by bordered caps.
- Plastic containers, made from LDPE of Ph.Eur. quality.
- Plastic bags Ecobag®, made of colourless, transparent three-layered film Cryovac M312.

Containers for small volume parenterals:
- Glass vials of colourless glass, sealed with elastomeric closures which are retained by bordered caps.
- Transparent plastic ampoules, made from LDPE.

As all packaging sizes contain the same ingredient these separate dossiers are considered as one product and they are assessed together. Where relevant, distinction between the containers is made in the text.

Pharmaceutical development
The product contains water for injections. It does not contain an active substance. No additional excipient is used either. No fundamental pharmaceutical development has been carried out, as it is a known standard preparation. An overfill is applied to comply with the Ph.Eur. requirement for extractable volume.

Manufacturing process
The manufacturing formula is identical for all containers as they only contain water. The process consists of filtering water for injections, filling it out into containers and terminal sterilisation. The sterilisation process is adjusted to the container material. The glass containers and the plastic bags are terminally sterilised by a standard process. For the LDPE containers terminal sterilisation at a nominal temperature of 121°C is not possible. In line with the 'Decision Tree for the Selection of Sterilisation methods' the sterilisation is therefore carried out at another temperature to achieve a $F_0 \geq 8$. Sufficient validation data have been presented. The alternative processes are acceptable.

Container closure system
The glass and LDPE containers all comply with the relevant Ph.Eur. requirements. Toxicity is therefore not to be expected. For the three-layered bags (Ecobag®) an extensive report is included. The Ecobag container, made from Cryovac M312 foil, has been authorised for many solutions for parenteral use. The bags are therefore also deemed suitable for the packaging of water for injections.

Microbiological attributes

The product is a sterile parenteral preparation. The filled glass containers are sterilised by an overkill method. The PE containers are formed, filled and sealed in a single work cycle. The integrity of the containers is checked at the end of the production process. The PE containers are sterilised at a lower temperature than standard. It is demonstrated that the sterility assurance level (SAL) is sufficient, and therefore this is acceptable. Stability studies demonstrate the microbiological quality of the product during the shelf-life.

Quality control of drug product
The specification is in line with the European Pharmacopoeia (Ph.Eur.*) monographs on for sterilised water for injections and for parenteralia. The specification includes tests for composition, dosage form, extractable volume, appearance, purity, degree of colouration, clarity and degree of opalescence, subvisible particles, subvisible particles, sterility, bacterial endotoxins, acidity or alkalinity, oxidisable substances, nitrates, sulphates, ammonium, calcium and magnesium and heavy metals. Ph.Eur. methods are applied where relevant. Batch analysis data have been provided on a sufficient number of production-scale batches. Compliance with the release requirements is demonstrated.

** 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.*

Stability of drug product
The products have been stored at 25°C/60% RH and 40°C/75% RH. The available data are sufficient to grant the following shelf-lives:

- 3 years in glass bottle, PE ampoule, glass vial en PE container; no special storage condition, do not refrigerate or freeze.
- 20 months in plastic Ecoba of 100 ml, store below 25°C, do not refrigerate or freeze.
- 2 years in plastic Ecobag >100 ml; store below 25°C, do not refrigerate or freeze.

The MAH sufficiently demonstrated that water loss from the glass vials and glass bottles will be negligible.

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

Water for injections has been available on the European market for many years. Preclinical data have been superseded by clinical experience and therefore no preclinical assessment report is available.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of water for injections 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

Water for injections is a well-known product with established tolerability.

Water voor injecties B. Braun is a parenteral formulation and does not contain an active substance; it is used exclusively as a dissolvent and diluent for injectable medicines. The quantitative composition of Water voor injecties B. Braun 100% m/v is identical to other established products on the market. Therefore, it may be considered as equivalent, with the same safety profile as known for these solvents. Extensive clinical experience with water for injections is considered to have demonstrated the therapeutic value of the compound.

Risk management plan

Water for injections is an established product, and there is now more than 10 years post-authorisation experience with its use. The safety profile 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 SPC. Additional risk minimisation activities have not been identified. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC

The content of the SPC approved during the national procedure is in accordance with those accepted for similar products and has been sufficiently adapted in line with the MEB's comments.

Readability test

The package leaflet has not been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. This is acceptable, as the product information of the added medicinal product is considered more relevant for the patient.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Water voor injecties B. Braun, solvent for parenteral use 100% m/v has a proven chemical-pharmaceutical quality and is a well-established product. Water for injections is used as a vehicle for the administration of the added medicinal product, and has been used in clinical practice for many years.

Since the current product is intended for parenteral use, no bioequivalence study is deemed necessary.

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

The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other water for injection products.

The Board followed the advice of the assessors. The MEB, on the basis of the data submitted, considered that sufficient quality has been demonstrated for the product, and has therefore granted a marketing authorisation. Water voor injecties B. Braun, solvent for parenteral use 100% m/v was authorised in the Netherlands on 12 April 2007.

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
C_{max}	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
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Change in shape of polyethylene plastic ampoules.	--	IB	1-6-2007	28-6-2007	Approval	N