CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Propofol YES 10 mg/ml and 20 mg/ml, emulsion for injection or infusion Yes Pharmaceutical Development Services GmbH, Germany

propofol

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 and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states 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.

EU-procedure number: NL/H/2284/001-002/DC
Registration number in the Netherlands: RVG 109300, 109303

5 September 2012

Pharmacotherapeutic group:	other general anesthetics
ATC code:	N01AX10
Route of administration:	intravenous
Therapeutic indication:	induction and maintenance of general anaesthesia; sedation for diagnostic and surgical procedures, alone or in combination with local or regional anaesthesia; sedation of ventilated patients in the intensive care unit
Prescription status:	prescription only
Date of authorisation in NL:	6 July 2012
Concerned Member States:	Decentralised procedure with DE, ES, FR, IT, UK
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

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, safety and efficacy data, the member states have granted a marketing authorisation for Propofol YES 10 mg/ml and 20 mg/ml, emulsion for injection or infusion from Yes Pharmaceutical Development Services GmbH. The date of authorisation was on 6 July 2012 in the Netherlands.

The product is indicated for:

- Induction and maintenance of general anaesthesia in adults and paediatric patients > 1 month of age (10 mg/ml)/> 3 years of age (20 mg/ml)
- Sedation for diagnostic and surgical procedures, alone or in combination with local or regional anaesthesia in adults and paediatric patients > 1 month of age (10 mg/ml)/> 3 years of age (20 mg/ml)
- Sedation of ventilated patients > 16 years of age in the intensive care unit.

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

After intravenous injection of propofol, onset of the hypnotic effect occurs rapidly. Depending on the rate of injection, the time to induction of anaesthesia is between 30 and 40 seconds. The duration of action after a single bolus administration is short due to the rapid metabolism and excretion (4 - 6 minutes).

This decentralised procedure concerns a generic application claiming essential similarity with the innovator products Diprivan-10 and Diprivan-20 (NL License RVG 11549 and RVG 18473) which have been registered in the Netherlands by AstraZeneca B.V. since 31 July 1987 and 28 February 1996, respectively. In addition, reference is made to Diprivan authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) 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 reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the ‘original’ authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. As Propofol YES 10 mg/ml and 20 mg/ml are products for parenteral use in aqueous solution, these are exempted for biostudy (NfG CPMP/EWP/QWP 1401/98). The current products can be used instead of their reference products.

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 generic 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
The active substance is propofol, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is a clear, colourless to slightly yellowish liquid. Propofol is very slightly soluble in water and miscible with hexane. Propofol does not show 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 active substance is controlled in accordance with the requirements of the Ph.Eur. monograph for propofol. Satisfactory batch analyses of three batches issued by the finished product manufacturer were provided.

Stability of drug substance
The active substance is stable for 36 months 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
Propofol YES 10 mg/ml and 20 mg/ml are white aqueous isotonic oil-in-water emulsions with osmolality of 309 to 311 mOsm/Kg and pH in the range of 6.0 – 8.5.

The emulsion for injection or infusion is packed in colourless Type I glass ampoules/vials with bromobutyl rubber stopper.
Propofol 10 mg/ml (1%) is available in 20 ml ampoules and 20 ml, 50 ml and 100 ml vials.
Propofol 20 mg/ml (2%) is available in 50 ml vials.

The excipients are: refined soya-bean oil, purified egg phospholipids, glycerol, sodium hydroxide (for pH-adjustment), water for injections.

Pharmaceutical development
The choice of excipients is justified and their functions explained. The excipients used are common for oily emulsions for parenteral use, and are the same as for the reference product except that no antimicrobial preservative is included in the proposed product. Information on formulation and manufacturing process

development was included. The choice of terminal sterilization was justified. No overage is used. A biowaiver has been granted based on demonstration of equivalence of globule size distribution on 9 batches of test product versus 3 batches of the reference product and based on the other physico-chemical comparable characteristics (rheological properties, composition, pH, etc.).

Compatibility
The compatibility of the drug product with 5% dextrose, 0.9% sodium chloride and 1% lidocaine hydrochloride solution has been investigated. The data is considered satisfactory and confirms the compatibility with the indicated diluents.

Manufacturing process
The description of the manufacturing process and flow chart are adequate. The manufacturing process has been adequately validated according to relevant European guidelines. The product is sterilized by terminal sterilization. Process validation data on the product has been presented for 3 commercial-scale batches per presentation, except for the 50 ml and 100 ml vials for which 2 and 1 batch has been validated. The provided validation data demonstrate that the manufacturing process is reproducible and able to constantly yield a product of adequate quality.

Control of excipients
The excipients comply with the requirements of the Ph. Eur. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, extractable volume, pH, free-fatty acid content, globule size, identity and content of propofol, degradation products, lysophosphatidylcholine, particulate contamination, sterility and bacterial endotoxins. The requirements for pH, free-fatty acid content, globule size and lysophasphatidylcholine at release are more tight compared to the shelf-life requirements. The shelf-life requirements are in line with the requirements of the BP monograph for propofol injection. The difference is supported by the stability data and acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on an adequate amount of commercial-scale batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for 3 batches per presentation stored at 30°C/75% RH (18 months), 40°C/75% RH (6 months) and 5°C/uncontrolled RH. The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in commercial packaging. The results of photostability studies have been provided.
All results remain within the requirements of the specification. The currently available 18 months stability data is sufficient to grant the proposed shelf-life of 18 months. The product should be stored below 30°C and it should be stored in the outer carton in order to protect from light as it is also mentioned in the SPC of the reference product. In addition, “do not freeze” is applicable.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Egg phospholipids is derived from animal origin (egg yolk powder). TSE conformity has been provided.

II.2 Non-clinical aspects

This product is a generic formulation of Diprivan, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

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 propofol 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

Propofol is a well-known active substance with established efficacy and tolerability.

Propofol YES 10 mg/ml and 20 mg/ml, emulsion for injection or infusion are parenteral formulations and therefore fulfils the exemption mentioned in the Note for Guidance on bioequivalence "5.1.6 parenteral solutions", which states that a bioequivalence study is not required if the product is administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Propofol YES 10 mg/ml and 20 mg/ml, emulsion for injection or infusion is entirely the same as the originator. Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current products can be used instead of their reference products.

Risk management plan

Propofol was first approved in 1995, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of propofol can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. 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. 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 decentralised procedure is in accordance with that accepted for the reference product Diprivan.

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 5 participants, followed by two rounds with 10 participants each. The majority of questions in this readability test could be answered without any significant problems. Overall, more than the required 90% (i.e. 18 out of 20 respondents) were able to find the requested information and thereof more than the required 90% were able to understand it. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Propofol YES 10 mg/ml and 20 mg/ml, emulsion for injection or infusion have a proven chemical-pharmaceutical quality and are generic forms of Diprivan-10 and Diprivan-20. Diprivan is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are 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 is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Propofol YES 10 mg/ml and 20 mg/ml with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 1 May 2012. Propofol YES 10 mg/ml and 20 mg/ml, emulsion for injection or infusion were authorised in the Netherlands on 6 July 2012.

The date for the first renewal will be: July 2016.

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