

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

**Propofol 20 mg/ml MCT/LCT Fresenius, emulsion for injection or
infusion in pre-filled syringe
Fresenius Kabi Nederland B.V., the Netherlands**

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.
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 110811

23 January 2014

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:	1 July 2013
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 (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 Propofol 20 mg/ml MCT/LCT Fresenius, emulsion for injection or infusion in ml pre-filled syringe from Fresenius Kabi Nederland B.V. The date of authorisation was on 1 July 2013 in the Netherlands.

Propofol 20 mg/ml is a short-acting intravenous general anaesthetic for:

- Induction and maintenance of general anaesthesia in adults, adolescents and paediatric patients > 3 years of age
- Sedation for diagnostic and surgical procedures, alone or in combination with local or regional anaesthesia in adults, adolescents and paediatric patients > 3 years of age
- 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 national procedure concerns a line extension for Propofol 20 mg/ml emulsion for injection or infusion in pre-filled syringe which will be injected into a vein by electric pumps. The composition of the emulsion is qualitatively and quantitatively the same as the approved Propofol 20 mg/ml MCT/LCT Fresenius emulsion (NL License RVG 26727), which is supplied in vials. This product has been registered since 5 November 2001 through a generic application claiming essential similarity with the innovator product Diprivan-20 (NL License RVG 18473) that has been registered in the Netherlands by AstraZeneca B.V. since 28 February 1996.

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. No bioequivalence study is necessary as the qualitative and quantitative composition of Propofol 20 mg/ml MCT/LCT Fresenius, emulsion for injection or infusion in pre-filled syringe is the same as that of the approved Propofol 20 mg/1 ml MCT/LCT Fresenius (presented in vials). Moreover, the quantitative composition of Propofol 20 mg/ml MCT/LCT is entirely the same as the originator (NfG CPMP/EWP/QWP 1401/98). The current product can be used instead of its reference product.

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.*). It is a colourless or very light yellow, clear liquid, which is very slightly soluble in water, and miscible with hexane and methanol.

The CEP procedure is used for all three suppliers of 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

CEPs have been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The quality of propofol from the three different manufacturers is controlled in compliance with the corresponding monograph of the Ph.Eur. The suitability of the monograph to test the drug substance has been verified by EDQM and is documented by the issue of certificates of suitability. Results of batch analysis were presented for each manufacturing site.

Stability of drug substance

For the first manufacturer, stability data have been provided in support of a retest period of 24 months at a temperature of 2 -8°C. The active substance from the second supplier is stable for 60 months at a temperature of 2-8°C.

For the third supplier, the re-test period granted is 36 months at a temperature not exceeding 25°C. 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 20 mg/ml MCT/LCT Fresenius is a sterile, white oil-in-water emulsion for intravenous infusion or injection. The drug product has pH 7.5-8.5 and osmolality of 300 mOsmol/kg. It is presented in 50 ml pre-filled cyclic olefin copolymer syringes closed with a luer-lock plug and halobutyl stopper.

The excipients are: refined soybean oil, medium chain triglycerides, glycerol, sodium hydroxide, oleic acid, purified egg lecithin, water for injection.

Pharmaceutical development

Propofol is practically insoluble in water. Lipophilic propofol is therefore dissolved directly in the oil phase of the oil-in-water emulsion. The inner phase is represented by both pharmaceutical grade soybean oil (long chain triglycerides: LCT), main ingredient of parenteral emulsions for more than 20 years, and

medium chain triglycerides (MCT). Further, egg lecithin is used as an emulsifier. It is considered an established standard in the production of parenteral lipid emulsions. The same applies to glycerol, used to make the drug product isotonic to blood. No overage is applied. According to the EU-Guideline on Plastic Immediate Packaging Materials CPMP/QWP/4359/03, extraction studies have been conducted. Results were satisfactory. Chemical and toxicological tests on the packaging materials showed results that meet the requirements. The choice of terminal sterilisation is justified. It was confirmed that physicochemical quality of the emulsion is maintained after autoclaving and that the required microbiological quality is achieved. The pharmaceutical development has been adequately performed and was described in sufficient detail.

Manufacturing process

The manufacturing process consists of preparation of the emulsion, filtration, filling and sterilisation. The manufacturing process including has been described in detail.

Process validation data on the product have been presented for three batches in accordance with the relevant European guidelines.

Control of excipients

The compendial excipients soy bean oil, medium chain triglycerides, glycerol, sodium hydroxide, nitrogen, and water for injection comply with the corresponding Ph.Eur. monographs.

Additional microbiological specifications apply to soy bean oil, medium chain triglycerides and glycerol.

Oleic acid complies with the Ph.Eur. monograph and an additional specification on bacterial endotoxins. An appropriate in-house specification for purified egg lecithin has been provided. All specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, pH, assay, density, osmolality, identification, mean fat droplet size, extractable volume and purity. The acceptance criteria comply with general pharmacopoeial requirements. Satisfactory method validation data are supplied.

Batch analytical data from 2 batches have been provided, demonstrating compliance with the specification.

Container closure system

The housing of the cyclo olefine syringe packaging system is manufactured from a cyclo olefine copolymer (COC) material consisting of amorphous, transparent copolymers based on cyclo olefins and linear olefins. The syringe housing material and the piston materials are siliconized. The tip caps and the plunger are made from a bromobutyl rubber. The piston rod has no contact to the solution. According to the EU-Guideline on Plastic Immediate Packaging Materials CPMP/QWP/4359/03, extraction studies have adequately been conducted. Extractables were evaluated toxicologically. From a toxicological point of view, there is no concern with regard to the leachables. Chemical tests on the packaging materials were performed and are in compliance with pharmacopoeial monographs (EP 3.1.4, EP 3.1.9, EP 3.2.2.1). Biocompatibility tests were carried out on raw housing materials. All specifications were met.

Stability of drug product

Stability data have been provided for two batches up to 18 months under long term conditions ($25^{\circ}\text{C} \pm 2^{\circ}\text{C}/40\% \text{ RH} \pm 5\% \text{ RH}$), 18 months intermediate ($30^{\circ}\text{C} \pm 2^{\circ}\text{C}/35\% \pm 5\% \text{ RH}$) and 6 months accelerated conditions ($40^{\circ}\text{C} \pm 2^{\circ}\text{C}/\leq 25\%$) for two batches. All results under long term as well as intermediate conditions are within the specification limits. Photostability data showed that the product is not sensitive to light. Based on these results, a shelf life of 2 years has been granted. The applicable storage condition is "Do not store above 25°C ".

Compatability

The compatibility of the drug product with the following solutions has been investigated after admixture in glass bottles and stored for 24 hour daylight at room temperature:

- Glucose 5 % (1+4)
- NaCl 0.09 % (1+4)

- Lidocain (Xylocain) 1 % (20+1)
Samples were analyzed initially and after 6 and 24 hours.

All results complied. No changes in physicochemical parameters could be observed.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
For purified egg lecithin appropriate virus validations have been performed. It is stated that no ruminant material is used, and thus compliance of the EDQM TSE regulation is fulfilled.

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. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the Board agreed that no further clinical studies are required.

Propofol 20 mg/ml MCT/LCT Fresenius, emulsion for injection or infusion in prefilled syringe is a parenteral formulations and 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 method and rate of administration of the product is the same as the currently approved product. Moreover, the quantitative composition of Propofol 20 mg/ml MCT/LCT is entirely the same as the originator (NfG CPMP/EWP/QWP 1401/98). 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 product can be used instead of its reference product.

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 post authorisation 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. A detailed European Risk Management Plan was not necessary for this product at the time of submission of the application.

Product information

SmPC

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Diprivan.

Readability test

Readability testing was performed for the package leaflet (PL) for Propofol 1% (10 mg/ml) MCT Fresenius emulsion for injection or infusion. For the PL for Propofol 2% (20 mg/ml) MCT Fresenius emulsion for injection or infusion a Bridging Report dated was submitted, which was acceptable.

Twenty-two participants were tested in total. Two participants were tested during a preliminary round of testing, 10 participants each were tested in the first and second round. The questionnaire contained 16 questions and was adequate. No changes were made to the PL based on the preliminary testing, the first or second round of testing as more than 90% of subjects were able to find the information within the PL and 90% could show that they understood and could act upon it. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Propofol 20 mg/ml MCT/LCT Fresenius, emulsion for injection or infusion in pre-filled syringe has a proven chemical-pharmaceutical quality and is a legitimate line extension to Propofol 20 mg/ml MCT/LCT Fresenius as presented in a vial. The product is a generic form of Diprivan-20, which 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. The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated with the reference product, and has therefore granted a marketing authorisation. Propofol 20 mg/ml MCT/LCT Fresenius, emulsion for injection or infusion in pre-filled syringe was authorised in the Netherlands on 1 July 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
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
LCT	Long-chain Triglyceride
MAH	Marketing Authorisation Holder
MCT	Medium-chain Triglyceride
MEB	Medicines Evaluation Board in the Netherlands
NfG	Note for Guidance
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SmPC	Summary of Product Characteristics
t _{1/2}	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
Addition of a secondary packaging site; addition of a site where batch control/testing takes place.	--	IA/G	24-6-2013	23-8-2013	Approval	N