CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Propofol Claris 10 mg/ml, emulsion for injection
Propofol Claris 20 mg/ml, emulsion for injection
Claris Lifesciences UK Limited, United Kingdom

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/1268/001-002/MR
Registration number in the Netherlands: RVG 31923, 32676

26 April 2010

Pharmacotherapeutic group:	other general anesthetics
ATC code:	N01AX10
Route of administration:	intravenous
Therapeutic indication:	induction and maintenance of complete anaesthesia; sedation of ventilated patients in Intensive care units; sedation for diagnostic and surgical procedures, alone or in combination with local or regional anaesthesia.
Prescription status:	prescription only
Date of first authorisation in NL:	27 March 2006/2 November 2006
Concerned Member States:	Mutual recognition procedure with AT, BE, DK, EE, EL, IT, LT, LU, LV, NO, PL, PT, SI; 10 mg/ml only- FI, SE and SK
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 Claris 10 mg/ml and 20 mg/ml, emulsion for injection from Claris Lifesciences UK Limited. The date of authorisation in the Netherlands was on 27 March 2006 for the 10 mg/ml product, and on 2 November 2006 for Propofol Claris 20 mg/ml.

The product is indicated as a short working intravenous complete anaestheticum for:

- the induction and maintenance of complete anaesthesia
- sedation of ventilated patients in Intensive care units
- sedation for diagnostic and surgical procedures, alone or in combination with local or regional anaesthesia

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

The hypnotic effect occurs quickly after the intravenous administration of propofol. Depending on the injection speed the time for induction of the anaesthesia is between 30 to 40 seconds. Because of fast metabolism and elimination the duration of effectiveness after a single bolus injection is 4-6 minutes.

This mutual recognition 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 Claris 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 these product types 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 or very light yellow liquid. Propofol is very slighty soluble in water, soluble in water for injections, and miscible with hexane and methanol.

The CEP procedure is used for the active substance for both manufacturers. 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 suitablity 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 new 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 active substance specification is considered adequate to control the quality. The drug substance is in line with the Ph.Eur., with additional requirements on the CEPs. A discussion on physico-chemical quality aspects of the drug substance that may influence quality of the drug product (e.g. polymorphy, particle size etc. of the drug substance) is not necessary, considering that the drug product is an emulsion and the drug substance is dissolved in the oil phase. Batch analysis results have been submitted, demonstrating compliance with the specification; in addition, batch results have already been assessed by the EDQM.

Stability of drug substance
Stability data on the active substance have been provided for 4 batches in accordance with applicable European guidelines. The batches were stored at 2-8°C for 36 months. Based on the data submitted, a retest period could be granted of 24 months when stored at 2-8°C.

** 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 Claris 10 mg/ml and 20 mg/ml are white oil-in-water emulsions with pH 7.0-8.5. The drug substance is present in lipid droplets in the emulsion. Due to the low solubility of propofol, the drug product is presented as an emulsion.

The emulsion for injection is packed in a glass vial (type II) with bromobutyl rubber stopper and plastic cap.
The 10 mg/ml product is available in vials containing 10 ml, 20 ml, 50 ml or 100 ml.
The 20 mg/ml product is available in a 50 ml vial.

The excipients are: refined soya-bean oil, glycerol, egg lecithin, sodium oleate, water for injection, sodium hydroxide (for pH adjustment).

Pharmaceutical development
The excipients used are common in the manufacture of the product. Development studies of the product have been performed and were extensively discussed. Bio-equivalence studies are not applicable, considering the dosage form. Essential similarity has been demonstrated between the products and the Dutch and UK innovator Diprivan (both strengths), based on the phycico-chemical comparable data (composition, pH, droplet size distribution, impurity profiles etc.). The sterilisation process is according to Ph. Eur. Compatibility with the container materials has been demonstrated, and also compatibility with claimed products in the SPC and typical materials containing these mixtures.

Manufacturing process
The product is manufactured by preparing the emulsion and heat sterilizing it according to Ph. Eur. The product is sterilised in its intended container. The manufacturing process has been sufficiently validated for three production batches.

Control of excipients
For glycerol, soya-bean oil, sodium hydroxide, water for injections and nitrogen Ph.Eur. specifications have been laid down. These specifications are acceptable. Adequate in-house specifications were established for the remaining excipients.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests and requirements for appearance, identity, globul size distribiution, pH, assay, fat content, glycerol content, egg lechitine content, degradation products (including lysophosphatidyl choline content, peroxide value, free fatty acids), bacterial enodotoxins, sterility, gastro-resistance. The limits for degradation products are qualified. The analytical methods have been adequately validated. Batch analysis results have been submitted of three batches of each strength, demonstrating compliance with the specification.

Compatability
Compatibility studies have been submitted for dilution of the product with several injection fluids (a.o. 5% glucose, 0.9% NaCl, combinations of these fluids and of lower percentage NaCl) and lidocaine 1% and 2%, covering those fluids mentioned in the SPC. Parameters studied were appearance (including phase separation), pH, assay, related substances. Containers containing the diluted fluids were: "plastic" bottles and glass vials, and also devices of IV sets. The mixtures with the infusion liquids appear to be compatible/stable untill approx. 30 hrs.

Stability of drug product
The product has been stored at 25°C/60% RH and 40°C/75% RH and 30°C/65%RH, up to at least two years at real time conditions and six months at the accelerated conditions, in the approved container. Based on the stability results, a shelf-life has been granted of two years, with the applicable storage conditions *store below 25°C* and *do not refrigerate or freeze*.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Egg lecithin is manufactured from Egg yolk, and audits are carried out on a regular basis. A short description is given of the production method. It is declared that the contract feed suppliers only deliver food from herbal origin to the hens. The steps taken to control and certify viral safety include checks on hebs, egg yolk processing and final processing. TSE and viral and microbiological risk for this excipient is negligible. Other than the egg lecithin there are no animal sourced substances used in the product.

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 Claris 10 mg/ml and 20 mg/ml, emulsion for injection 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 Claris 10 mg/ml and 20 mg/ml, emulsion for injection 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

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. Three rounds of testing have been performed: a preliminary study and a main study consisting of two rounds were carried out with 10 participants.
The developed questionnaire contained 14 questions specific to the product. The questions addressed all key safety issues and concerns.
Round 1 did not bring about any further modifications and therefore round 2 of the main study was done with the same PIL version as round 1. Round 2 did not result in new or further results either.
The readability test itself and the evaluation report are of an acceptable quality. There were sufficient questions about the critical sections. In the test it was easy to determine which results are linked to which conclusions. The conclusions are clear, concise and clearly presented.
Overall, it can be concluded that the readability of the leaflet is of an acceptable level. Furthermore, the following areas have been sufficiently covered: traceability, comprehensibility and applicability. Every question was answered correctly by 100% of the participants. Furthermore, every text passage could be found by 100% of the participants. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Propofol Claris 10 mg/ml and 20 mg/ml, emulsion for injection 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 and are in agreement with other propofol containing products.

The Board followed the advice of the assessors. Propofol Claris 10 mg/ml and 20 mg/ml, emulsion for injection were authorised in the Netherlands on on 27 March 2006 and 2 November 2006, respectively.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Propofol Claris 10 mg/ml and 20 mg/ml, emulsion for injection with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 19 January 2009.

A European harmonised birth date has been allocated (8 November 1995) and subsequently the first data lock point for propofol is 30 November 2012. The first PSUR will cover the period from January 2009 to November 2012, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 30 July 2013.

The following post-approval commitment has been made during the procedure:

Quality - medicinal product

- The MAH committed to submit the signed document on the revised quality control method before marketing the products.

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