COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Propofol BioQ Pharma 10 mg/ml, emulsion for infusion in administration system

(propofol)

NL/H/2284/003/DC

Date: 27 February 2019

This module reflects the scientific discussion for the approval of Propofol BioQ Pharma 10 mg/ml, emulsion for infusion in administration system. The procedure was finalised at 13 September 2018. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Propofol BioQ Pharma 10 mg/ml, emulsion for infusion in administration system from BioQ Pharma Ltd.

The product is indicated for:

- Induction and maintenance of general anaesthesia in adults, adolescents and children ≥ 40 kg.
- Sedation for diagnostic and surgical procedures, alone or in combination with local or regional anaesthesia in adults, adolescents and children ≥ 40 kg.
- 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 SmPC.

This decentralised procedure concerns a line extension to the previously approved Propofol BioQ Pharma 10 mg/ml and 20 mg/ml emulsion for injection or infusion. The first marketing authorisation was granted on 6 July 2012. It is submitted in accordance with Article 10 (3) of Directive 2001/83/EC as amended (hybrid application) as it concerns a different pharmaceutical form (emulsion for injection in administration system).

The application refers to reference product Diprivan 10 mg/ml, solution for injection by Aspen Pharma Trading Limited, Ireland (AstraZenaca up to 2017), registered in The Netherlands since 28 February 1996.

The concerned member states (CMS) involved in this procedure were Germany, France, Spain, Italy and the United Kingdom.

II. QUALITY ASPECTS

II.1 Introduction

Propofol BioQ Pharma is a white aqueous isotonic oil-in-water emulsion for infusion in an administration system. Each ml emulsion for infusion contains 10 mg propofol. Each pre-filled infusion pump (administration system) contains a 50 ml cartridge corresponding to 500 mg propofol. The osmolality of the emulsion is 285-320 mOsm/kg and pH is in the range of 6.0-8.5.

Each pack contains one pre-filled infusion pump (administration system). Each pre-filled infusion pump contains 50 ml emulsion for infusion in a colourless type I glass cartridge with teflon-coated bromobutyl plunger and polypropylene stopper.

The propofol-filled Weight/Dose Dispenser (WDD) is a single-use, single-dose, pre-filled electronic infusion pump. It is intended for the delivery of propofol based on the weight of the patient and the dose to be delivered. The drug and fluid path are sterile.

The finished dispenser consists of a barrel/cartridge that contains no less than 50 ml of 10 mg/ml Propofol emulsion and electromechanical pump module to deliver the emulsion per the body weight and dosage required.
Principle of operation of the finished product (i.e. dispensing device) includes a motor assembly that delivers fluid using peristaltic displacement at known patient body weight and the required dose as set by the health care practitioner.
The finished medicinal product (i.e. the assembled dispensing device) is, prior to use, activated immediately by removal of the pull tab, i.e. joined strips covering the administration line and the barrel/cartridge, so that the cartridge and the sterile administration line are opened at the same time.

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

II.2 Drug 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 Ph.Eur.

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 specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

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.

II.3 Medicinal Product

Pharmaceutical development

Emulsion in prefilled cartridge (intermediate)

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. 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 sterilisation of the emulsion in the prefilled cartridge 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.).

Assembled dispensing device

The finished product assembly was developed with the approach that the sterile, propofol-filled and complete container closure system can be assembled into an electromechanical dispenser. The design requirement was such that once the finished product is assembled and packaged, the end user (the healthcare practitioner) would receive a ready-to-use unit which would require minimum number of steps for activation and use.

Preservation of sterility is ensured since the drug emulsion and sterile device components (tubing) remain independently sealed, based on validation data on a.o. container closure integrity tests.

A CE certificate of the Notified Body is included. An adequate updated EU human factors user study is included, based on the newly designed interface.

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 sterilised by terminal sterilisation. Process validation data on the product has been presented for three commercial-scale batches. 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, bacterial endotoxins and device performance testing (flow rate/dose accuracy/dose uniformity and pull tab force). The requirements for pH, free-fatty acid content, globule size and lysophosphatidylcholine at release are more tight compared to the shelf-life requirements. The shelf-life requirements are in line with the requirements of the British Pharmacopeia 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 three production batches, demonstrating compliance with the release specification.

Container closure system

The prefilled cartridge and the (assembled) dispensing device are described, including the materials. Adequate specifications are provided for glass barrel, polypropylene stopper assembly and rubber plunger of the cartridge. The names of the suppliers are stated. Adequate specifications are also provided for the device.

Stability of drug product

Stability data on the product has been provided for 3 batches stored at 30°C/75% RH (12 months), 40°C/75% RH (6 months) and 5°C/uncontrolled RH (12 months). 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. On the basis of the stability data a shelf life of 1 year is granted. The product should be stored in the outer carton in order to protect from light as it is also mentioned in the SmPC 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.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Propofol BioQ Pharma has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Propofol BioQ Pharma is intended for hybrid substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a hybrid formulation of Diprivan which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

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 member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

Propofol BioQ Pharma 10 mg/ml, emulsion for infusion in administration system is a parenteral formulation 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 BioQ Pharma 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 product can be used instead of its reference product.

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Propofol BioQ Pharma.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	- Misuse of propofol - Renal impairment - Bradycardia - Convulsion in patients with epilepsy and epileptiform movements - Patients with disorders of lipid metabolism - Propofol infusion syndrome - Hypotension, airway obstruction, oxygen desaturation
Important potential risks	- Involuntary movements - Postoperative unconsciousness - Growth of micro-organisms - Overdose in patients < 40 kg
Missing information	- Use in children/neonates (potential for significantly reduced clearance and overdose) - Use in pregnancy

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Diprivan. No new clinical studies were conducted. Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The MAH has bridged the Package Leaflet (PL) of the proposed medicinal product to the original user test performed for its own registered 10 mg/ml strength. The bridging report compares design and lay-out and key safety messages between parent and daughter PIL. The PILs are considered sufficiently similar, and bridging is therefore deemed acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Propofol BioQ Pharma 10 mg/ml, emulsion for infusion in administration system has a proven chemical-pharmaceutical quality and is a hybrid form of Diprivan 10 mg/ml, solution for injection. 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. A biowaiver has been granted.

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 BioQ Pharma with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 13 September 2018.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse