COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Paracetamol Viaflo 10 mg/ml solution for infusion
(paracetamol)

NL/H/5110/001/DC

Date: 27 January 2022

This module reflects the scientific discussion for the approval of Paracetamol Viaflo 10 mg/ml solution for infusion. The procedure was finalised on 9 June 2021. 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 Paracetamol Viaflo 10 mg/ml solution for infusion, from Baxter Holding B.V.

The product is indicated for the short-term treatment of moderate pain, especially following surgery and for the short-term treatment of fever, when administration by intravenous route is clinically justified by an urgent need to treat pain or hyperthermia and/or when other routes of administration are not possible. This medicinal product is indicated in adults, adolescents and children weighing more than 33 kg. A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Perfalgan 10 mg/ml solution for infusion which has been registered in France by Bristol-Myers Squibb since 2001 by the procedure FR/H/0197/001/MR. In The Netherlands the innovator product has been registered since 2001, but was withdrawn in 2012.

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Cyprus, Germany, Denmark, Greece, Estonia, Finland, France, Ireland, Italy, Luxembourg, Malta, Norway, Portugal, Spain and the United Kingdom (Northern Ireland).

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Paracetamol Viaflo is a solution for infusion. The solution is clear, colourless to slightly yellowish and free from visible particles with a pH of 5.0 – 6.5 and osmolality of 270 to 310 mOsm/kg.

One ml solution contains as active substance 10 mg paracetamol. Each bag of 100 ml contains 1000 mg paracetamol.

The solution for infusion is packed in 100 ml polyethylene/polyamide/polypropylene plastic bags, provided with one polyethylene dummy non-accessible port and one polyethylene administration port with clear/foil overpouch.

The excipients are: L-cysteine hydrochloride monohydrate (E920), disodium phosphate (E339), hydrochloric acid (for pH adjustment) (E507), mannitol (E421), sodium hydroxide (for pH adjustment) (E524) and water for injections.

II.2 Drug Substance

The active substance is paracetamol, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or almost white crystalline powder, sparingly soluble in water, freely soluble in ethanol (96%) and very slightly soluble in methylene chloride. Paracetamol shows polymorphism but only polymorphic form I is manufactured. The drug substance is dissolved in the final drug product.

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. Purified water is used in the last step of the drug substance synthesis.

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. and the CEP. The drug product manufacturer has an additional test for solubility, endotoxins and bioburden. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three batches.

Stability of drug substance

The active substance is stable for 66 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

The development of the product has been clearly described. The development was based on characteristics of the reference product Perfalgan 10 mg/ml solution for infusion by Bristol Meyers Squibb Pharmaceuticals Ltd., the related quality target product profile and critical quality attributes, experience of the drug product manufacturer with the excipients and the drug substance characteristics. Although no compatibility studies were performed for the

drug substance and excipients, the choice of excipients is justified by comparison with the reference product, stability studies provided, and their functions were adequately explained. The order of excipient addition, impact of inert gas sparging of the bulk and effect of pH was studied and optimised. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process consists of eight phases: weighing, mixing, bioburden reducing filtration, filling, racking, terminal sterilization, inspection and sampling, packing and palletization and finished product release. The Viaflo bag, including the port system, is manufactured in one process with the bag filling. Extensive extractables and leachables studies were provided in support of the container closure system. The Viaflo port assembly is sterilised by gamma irradiation using a dose of 25 kGy. A radiation dose mapping validation study is provided. The moist heat terminal sterilisation process is performed at 118°C and deviates from the reference sterilisation cycle as provided in the Ph.Eur. 5.1.1 because the softening point of the polyethylene material of the non-accessible single access port system is near 121°C. Moist heat sterilization process validation data on four validation batches with maximum capacity and four batches with minimum capacity has been provided. The manufacturing process has been validated according to relevant European/ICH guidelines.

Control of excipients

The excipients comply with the Ph.Eur. requirements and are additionally tested on bioburden and bacterial endotoxins. These 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 characteristics (color, clarity, visible particles), Paracetamol identity by HPLC and UV, L-Cysteine identity by HPLC, pH, extractable volume, osmolality, particulate matter, assay of Paracetamol, assay of L-cysteine hydrochloride monohydrate, assay of mannitol, related substances, bacterial endotoxins, sterility, weight loss and package integrity leak test. The weight loss and package integrity leak test are only performed during stability testing. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three batches from the proposed production site have been provided, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product have been provided for three production scale batches stored at 25°C/40% RH (18 months) and 40°C/25% RH (six months) in accordance with applicable European guidelines demonstrating the stability of the product. The conditions used in the stability studies are according to the ICH stability guideline (i.e. for finished products packaged in semi-permeable containers). The dosage forms were packaged in the container closure system proposed for marketing. The accelerated and long term stability studies demonstrate that no clear trends are observed for most of the tested parameters and the

variability is low. Only for particulate matter, total of impurities and weight loss, a slight increase is observed over time at both storage conditions. The results were all well within the proposed acceptance criteria for all batches.

On basis of the data submitted, a shelf life was granted of two years. Photostability studies were performed in accordance with ICH recommendations and showed that that product is stable when exposed to light. Also a freeze thaw cycling study was provided and it was concluded that thermal cycling three times through two days at -20°C followed by two days at 40°C / not more than 25% RH does not negatively impact the drug product. However, the proposed label claim "Do not refrigerate or freeze" is acceptable as this label claim is comparable with the reference product.
The proposed in use claim "From a microbiological point of view, unless the method of opening precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user. Following the opening of the overpackaging, the product must be used immediately." is acceptable.

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.4 Discussion on chemical, pharmaceutical and biological aspects

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

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Paracetamol Viaflo is intended for generic 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 generic formulation of Perfalgan 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

Paracetamol 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.

Bioequivalence studies are not required since the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product.

IV.2 Pharmacokinetics

Paracetamol Viaflo 10 mg/ml solution for infusion 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 Paracetamol Viaflo 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 Paracetamol Viaflo.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	- Medication error leading to an accidental overdose (overdose

	due to confusion between mg and ml in neonates and infants, and overdose in underweight adult patients)
Important potential risks	- None
Missing information	- Lack of data on use in premature neonates

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 Perfalgan. No new clinical studies were conducted. The MAH demonstrated through that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) 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 language used for the purpose of user testing the PL was English.
The test consisted of: a pilot test with five participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

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 Paracetamol Viaflo with the

reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 9 June 2021.

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