COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Paracetamol Baxter 10 mg/ml, solution for infusion
(paracetamol)

NL/H/5013/001/DC

Date: 19 August 2021

This module reflects the scientific discussion for the approval of Paracetamol Baxter 10 mg/ml, solution for infusion. The procedure was finalised at 26 February 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 Baxter 10 mg/ml, solution for infusion, from Baxter 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.

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 European reference product (ERP) Perfalgan 10 mg/ml solution for infusion registered by Bristol-Myers Squibb in Italy. Perfalgan was registered in the Netherlands on 22 January 2001 via a mutual recognition procedure (FR/H/0197/001/MR). The marketing authorisation of Perfalgan in the Netherlands has been withdrawn since 1 September 2012.
The concerned member states (CMS) involved in this procedure were Austria, Belgium, Cyprus, Germany, Denmark, Greece, Finland, France, Ireland, Italy, Luxembourg, Norway, Portugal, Spain, Sweden 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 Baxter is a clear, colourless to slightly yellowish solution for infusion, free from visible particles. The osmolality is 270 to 310 mOsm/kg and pH 4.5 – 6.5. 1 ml solution contains 10 mg paracetamol.

There a two fill volumes, namely 50 ml and 100 ml. The solutions for infusion are packed in type II clear glass vial with chlorobutyl rubber stopper and red (50 ml fill volume) or blue (100 ml fill volume) colour aluminium flip-off cap.

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 injection.

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 and is sparingly soluble in water. Paracetamol has no stereoisomers. As the product concerned by this application is a solution, particle size and polymorphism are not of concern.

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 proposed specification is in line with the CEP with additional requirements for microbial contamination.

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 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 choices of the packaging are justified in relation to the reference product. Terminal sterilisation is applied using Ph. Eur. reference conditions. Furthermore, the order of excipient addition has been established A pH of 4.5-6.5 was found to be suitable for the formulation. In addition, the effect on temperature on the bulk solution, the bulk hold time, filter compatibility, tubing selection and prototype development batches stability were investigated. No overages are used in the manufacture of the drug product formulation.

Manufacturing process
The solution for infusion is manufactured by dispensing and mixing the raw materials, filtering of the bulk solution, filling and sealing of the vials, followed by terminal sterilisation.

The product is manufactured using conventional manufacturing techniques. The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post authorisation.

Control of excipients
The excipients comply with Ph.Eur. requirements. 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 description, identity, extractable volume, pH, osmolality particulate matter, assay, an impurity, related substances, bacterial endotoxins and sterility. The release and shelf-life acceptance limits are not identical. However, limits in the specification have been justified and are considered appropriate for adequate quality control of the product. A risk evaluation concerning the presence of nitrosamine impurities in the product was provided. No risk for nitrosamine was found. The analytical methods have been adequately described. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from six pilot scale batches (three for each fill volume) from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided on three pilot scale batches per fill volume stored at 25°C/60% RH (18 months for the 50 ml fill volume, 24 months for the 100 ml fill volume) and 40°C/75% RH (6 months for both). The conditions used in the stability studies are according to the ICH stability guideline. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. On basis of the data submitted, a shelf life was granted of 24 months. It is recommended not to refrigerate or freeze this medicinal product. Developmental stability data has been provided demonstrating that the product remains stable for 48 hours following dilution, when stored at 20-25˚C, although immediate use is recommended.

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 Baxter 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 Baxter 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.

IV.2 Pharmacokinetics

Paracetamol pharmacokinetics is linear up to 2 g after single administration and after repeated administration during 24 hours. The volume of distribution of paracetamol is approximately 1 l/kg. Paracetamol is not extensively bound to plasma proteins. Paracetamol is metabolised mainly in the liver following two major hepatic pathways: glucuronic acid conjugation and sulfuric acid conjugation.
In adults, about 60% of the drug undergoes glucuronidation and 35% undergoes sulfation. Children have limited capacity for glucuronidation and a large proportion of paracetamol is conjugated to sulfate. The metabolites of paracetamol are mainly excreted in the urine and less than 5% is eliminated unchanged. The plasma half-life is 2.7 hours.

Biowaiver
Paracetamol Baxter 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 authorised reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Paracetamol Baxter 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 Baxter.

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

Important identified risks	– Medication error leading to an accidental overdose (overdose due to confusion between ml and mg 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.

As additional risk minimisation measures for dosing errors the following measures are proposed:

- A dosing tool - To minimise the risk of overdose due to confusion between ml and mg in neonates and infants, and overdose in underweight adult patients by providing

a tool which summarises key dosing instructions and a slider to aid healthcare professionals in determining appropriate weight-based dosing of paracetamol.
- A poster - To minimise the risk of overdose due to confusion between ml and mg in neonates and infants by providing a poster which summarises the weight-based administration protocol in that population of patients.

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. 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 20 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

Paracetamol Baxter 10 mg/ml, solution for infusion has a proven chemical-pharmaceutical quality and is a generic form of Perfalgan 10 mg/ml, solution for infusion. Perfalgan 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 Paracetamol Baxter with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 26 February 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