COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Paracetamol pxgpharma 500 mg film-coated tablets (paracetamol)

NL/H/5594/001/DC

Date: 8 December 2023

This module reflects the scientific discussion for the approval of Paracetamol pxgpharma 500 mg film-coated tablets. The procedure was finalised on 19 July 2023. 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
BCS	Biopharmaceutics Classification System
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
EMA	European Medicines Agency
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
RMS	Reference Member State
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 pxgpharma 500 mg film-coated tablets from PXG Pharma GmbH (Germany).

The product is indicated for: short-term symptomatic treatment of mild to moderate pain and/or fever. Paracetamol pxgpharma 500 mg is indicated in adults, adolescents and children with body weight from 22 kg (over 6 years of age).

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this decentralised procedure, essential similarity is proven between the new product and the innovator product Panodil 500 mg tablets (film-coated tablets) which has been registered in Denmark by GlaxoSmithKline Consumer Healthcare A/S since 14 August 1974. The justification to use this ERP is based on information received from Denmark.

The concerned member states (CMS) involved in this procedure were Czechia, Estonia, Hungary, Lithuania, Latvia, Romania and Slovakia.

II. QUALITY ASPECTS

II.1 Introduction

Paracetamol pxgpharma 500 mg is a white to off-white coloured, caplet shaped film-coated tablets with flat-edges. It is debossed with “PARA500” on one side and score line on the other side.

Each film-coated tablet contains 500 mg paracetamol.

The excipients are:
Tablet core - pregelatinized maize starch, povidone K-30, sodium maize starch glycolate (type-A) and stearic acid (E570).
Film-coating - hypromellose (E464) and macrogol 400 (E1521).

Pack sizes of 10 film-coated tablets are packed in one clear, transparent polyvinyl chloride (PVC)/aluminium blister pack in an outer carton box.

Pack sizes of 20, 30 and 50 film-coated tablets are packed in two, three and five clear, transparent polyvinylidene chloride (PVDC) coated PVC/aluminium blister packs in an outer carton box.

Pack sizes of 24 film-coated tablets are packed in white opaque high density polyethylene (HDPE) bottle packs with white polypropylene closure in an outer carton box.

Pack sizes of 100, 300, 500 and 1000 film-coated tablets are packed in white opaque HDPE bottle packs with white polypropylene closure.

II.2 Drug Substance

The active substance is paracetamol, an established active substance described in the Ph.Eur. The active substance is a white or almost white crystalline powder. Paracetamol is sparingly soluble in water, freely soluble in ethanol (96%) and very slightly soluble in methylene chloride.

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. The CEP contains additional tests for bulk density, sieve analysis and identification. In addition, the MAH has demonstrated the absence of microbial growth in the drug substance to justify the lack of a routine test for the control of microbiological quality in the specification of the drug substance. Batch analytical data demonstrating compliance with this specification have been provided for three full scaled batches.

Stability of drug substance

The active substance is stable for 5 years if 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 development of the product has been described, the choice of excipients is justified and their functions explained. The choices of packaging and manufacturing process are justified in relation to the innovator. Sufficient information regarding the physicochemical properties of the drug substance, the

suitability of the excipients and the drug product for paediatric patients and the manufacturing process development have been included.

For this application, a class 1 BCS-based biowaiver is applicable. Comparative dissolution profiles in water and buffer at 4 different pHs without surfactants are included demonstrating similarity in dissolution. The proposed QC dissolution method is acceptable and the discriminating power of the QC dissolution method has been demonstrated.

Manufacturing process

Tablets are manufactured by wet granulation followed by drying, blending, lubrication, compression and coating. The product is manufactured using conventional manufacturing techniques. The manufacturing process has been validated according to relevant European guidelines. A 12-month holding time for the bulk product (core tablets) has been proposed and has been properly justified based on experimental data in line with the EMA Guideline on Manufacture of the finished dosage form. Process validation data on the product have been presented for three pilot scaled batches and three commercial batches in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with Ph.Eur. requirements and additional tests for functionality-related characteristics. 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 appearance, dimensions, identification, average weight, moisture content, uniformity of dosage units by mass variation, dissolution, assay, subdivision of tablets, related substances and microbiological quality. 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 and applying the principles outlined in the “Assessment report Procedure under Article 5(3) of Regulation EC (No) 726/2004 (EMA/369136/2020)” as well as information on elemental impurities in the drug product as per ICH Q3D have been submitted and are acceptable.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data on three commercial batches 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 for three commercial batches packed in the HDPE bottles, PVC/Al blisters and PVDC/Al blisters and stored at 25°C / 60% RH. The stability was tested in accordance with applicable European guidelines. On basis of the data submitted, a shelf life was granted of 36 months without any special storage condition. Photostability studies were performed on one pilot batch in accordance with ICH recommendations and showed that the product is stable when exposed to light. Bulk stability studies have been

performed on three pilot batches stored in LPDE bags at 25°C / 60% RH for up to 60 months. All results were found within the proposed limits for all evaluated test parameters.

In-use stability data have been provided for one pilot batch packed in HDPE bottle and stored at 25°C / 60% RH. The results show that the product remains stable for 6 months. All results were within the proposed limits indicating that no deterioration is expected. An in-use shelf-life period does not have to be stated in the SmPC.

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 pxgpharma 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 pxgpharma is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of paracetamol which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was 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 member states agreed that no further clinical studies are required.

For this generic application, no *in vivo* bioequivalence studies were performed. A BCS class I biowaiver has been requested.

IV.2 Pharmacokinetics

Paracetamol is a long-standing drug and its safety/efficacy profile and use are well established. Since Paracetamol pxgpharma 500 mg tablets are immediate release, solid pharmaceutical forms for oral administration and systemic action, the approach of the Biopharmaceutics Classification System (BCS) biowaiver is applicable. Based on this, Paracetamol is considered as BCS class I active pharmaceutical ingredient according to the regulations for medicinal products CPMP/EWP/QWP/1401/98 REV. 1/ Corr.

<u>BCS-based Biowaiver</u>
The following general requirements must be met where a BCS-based biowaiver is claimed, according to the EMA Bioequivalence guideline:

a. the drug substance has been proven to exhibit high solubility and complete absorption and
b. either very rapid (> 85 % within 15 min) or similarly rapid (85 % within 30 min) *in vitro* dissolution characteristics of the test and reference product has been demonstrated considering specific requirements and
c. excipients that might affect bioavailability are qualitatively and quantitatively the same. In general, the use of the same excipients in similar amounts is preferred.

The MAH has provided the dissolution data of three pilot scale batches of Paracetamol pxgpharma and one batch of Panodil in 900 mL media, at 4 different pH's (0.1N HCl pH 1.2, acetate buffer pH 4.5 and phosphate buffer pH 5.8 (QC media) and pH 6.8) as well as in water. The size of the batches and test methodology comply with the EMA Guideline on Investigation of the Bioequivalence. The dissolution data show that ≥85% of the drug product was dissolved within 15 minutes in all media. Therefore, dissolution profiles may be accepted as similar without further mathematical evaluation as per EMA Guideline on Investigation of Bioequivalence.

Furthermore, considering composition, there are no excipients present which might affect the bioavailability. All criteria for the biowaiver are met and with this the BE is acceptable.

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 pxgpharma 500 mg.

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

Important identified risks	None
Important potential risks	None
Missing information	None

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 Panodil. No new clinical studies were conducted. A BCS class I biowaiver has been granted. 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 test consisted of a pilot test with two 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 pxgpharma 500 mg film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Panodil 500 mg tablets. Panodil is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

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 pxgpharma 500 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 19 July 2023.

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
-	-	-	-	-	-