COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Paracetamol Pharmaclan 500 mg film-coated tablets
(paracetamol)

NL/H/5231/001/DC

Date: 21 January 2022

This module reflects the scientific discussion for the approval of Paracetamol Pharmaclan 500 mg film-coated tablets. The procedure was finalised on 3 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

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
EDQM	European Directorate for the Quality of Medicines
ERA	Environmental Risk Assessment
ERP	European Reference Product
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 Pharmaclan 500 mg film-coated tablets, from Pharmaclan s.r.o.

The product is indicated for short-term symptomatic treatment of mild to moderate pain and/or fever.

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) 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 Germany, Spain, Hungary and Ireland.

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

II. QUALITY ASPECTS

II.1 Introduction

Paracetamol Pharmaclan is a white to off-white coloured, caplet shaped film-coated tablet with flat-edges debossed with “PARA500” on one side and score line on the other side. The tablet can be divided into two equal doses.

Each film-coated tablet contains 500 mg paracetamol.

The film-coated tablets are packed in:

- Clear, transparent PVC/Aluminium blister pack in an outer carton box, or;
- Clear, transparent PVdC coated PVC/Aluminium blister pack in an outer carton box, or;
- White opaque HDPE bottle packs with white polypropylene closure.

The excipients are:
Tablet core - pregelatinised maize starch, povidone K-30, sodium maize starch glycolate (type A) and stearic acid (E570).

Film-coating - hypromellose (E464), macrogol 400 (E1521).

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. 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 in line with the Ph.Eur., the CEP and contains additional tests for bulk density, sieve analysis and identification. The specification is acceptable in view of the various European guidelines. Compliance with ICH Q3C has been stated. 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 the drug substance specification have been provided on three full scaled batches. The presented batch data comply with the specification requirements.

Stability of drug substance
The active substance is stable for five years when stored in double polyethylene bags, placed in either polyethylene bags or fibre or polyethylene drums. 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 are 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.

Comparative dissolution profiles in water and buffer at four different pH's 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. The MAH has justified the absence of a bioequivalence study based on a class I biopharmaceutics classification system (BCS)-based biowaiver. This will be further discussed in section IV on the clinical aspects.

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 adequately described and validated according to relevant European guidelines.

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 appearance, 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 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 stored at 25°C/60% RH have been provided for three commercial batches packed in HDPE bottles (36 months) and for three commercial batches packed in aluminium blisters (36 months). All results were found within the proposed limits for all evaluated test parameters. The conditions used in the stability studies are according to the ICH stability guideline. 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 (up to 60 months). All results were found within the proposed limits for all evaluated test parameters.

On basis of the data submitted, a shelf life was granted of 36 months and 30 months for the drug product packed in the HDPE bottle and in aluminium blisters, respectively. The labelled storage condition is: 'This medicinal product does not require any special storage conditions.'

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Paracetamol Pharmaclan 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 Pharmaclan 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 Panodil 500 mg Tablets 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

BCS-based biowaiver

The MAH requested a BCS-based biowaiver. The BCS-based biowaiver approach is meant to reduce *in vivo* bioequivalence studies, i.e., it may represent a surrogate for *in vivo* bioequivalence. *In vivo* bioequivalence studies may be exempted if an assumption of equivalence in in vivo performance can be justified by satisfactory *in vitro* data.

The following requirements set in the EMA *Guideline on the Investigation of Bioequivalence* are met:

- The drug substance has been proven to exhibit high solubility and complete absorption (BCS-class I);
- 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.
- 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 justification based on class 1 BCS-based biowaiver is considered sufficient, therefore, a biowaiver has been granted.

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 Pharmaclan.

Table 1. 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-based 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 language used for the purpose of user testing the PL was English. The test consisted of: a pilot test with two participants, followed by two rounds with ten 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 Pharmaclan 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 Pharmaclan with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 3 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