COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Paracetamol PharmaMatch 500 mg, oval, tablets (paracetamol)

NL License RVG: 127800

Date: 15 November 2022

This module reflects the scientific discussion for the approval of Paracetamol PharmaMatch 500 mg, oval, tablets. The marketing authorisation was granted on 14 January 2022. 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 Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Paracetamol PharmaMatch 500 mg, oval, tablets from Pharmamatch B.V.

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 national procedure concerns a generic application claiming essential similarity with the innovator product Panadol gladde tablet 500 mg, tablets (NL RVG 18550) which has been registered in The Netherlands by GlaxoSmithKline Consumer Healthcare B.V. since 24 July 1995.

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

II. QUALITY ASPECTS

II.1 Introduction

Paracetamol PharmaMatch is a white, capsule shaped tablet with “500” debossed on one side and plain on the other. Each tablet contains 500 mg paracetamol.

The tablets are packed in transparent or white, opaque PVC/aluminium blisters or HDPE bottles with child resistant plastic caps.

The excipients are: povidon K30 (E1201), pregelatinised corn starch, sodium starch glycolate (type A) and stearic acid (E570).

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 soluble in methylene chloride. Polymorphic form I is consistently produced.

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 European Pharmacopoeia.

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 specification is also in line with the CEP and additional tests for particle size distribution and microbial quality have been included. The specification is acceptable in view of the various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for three commercial scale batches.

Stability of drug substance

The active substance is stable for five years 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, as are the choices of packaging and the manufacturing process. The polymorphic form of the drug substance was shown not to change upon storage. Instead of submitting a study on bioequivalence, the MAH applied for a BSC (Biopharmaceutics Classification System)-based biowaiver. This is deemed acceptable as sufficient information on solubility and stability of the active substance in the solubility media has been provided. The proposed quality control (QC) dissolution method is acceptable however, the discriminating power of the QC dissolution method has not been demonstrated. This is not an issue considering the high solubility and very rapid dissolution of the active substance.

Manufacturing process

The manufacturing process consists of wet granulation of granules containing the drug substance, followed by drying, sifting, blending and lubrication before compression. This manufacturing process is considered as standard. The manufacturing process is described in sufficient detail and is validated according to relevant European guidelines. Validation data for three consecutive commercial batches have been provided and the process is considered adequately validated.

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, identification, average weight, weight variation, friability, thickness, hardness, disintegration time, water content, dissolution, assay, uniformity of dosage units by mass variation, related substances and microbiological quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

The risk evaluation concerning the presence of nitrosamine impurities in the product and subsequent principles has been provided. In addition, information on elemental impurities in the drug product and eventual control measures has been provided and no further controls are required. Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three commercial scale 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 from three commercial batches per strength stored under long-term stability conditions at 25°C/60% RH (up to 36 months) and 40°C/75% RH (6 months). This is in accordance with applicable European guidelines. Bulk stability studies have been performed on three pilot and three commercial batches stored in low-density polyethylene (LPDE) bags at 25°C / 60% RH for up to 12 months. All results were found within the proposed limits for all evaluated test parameters. Photostability studies showed that the product is stable when exposed to light. On basis of the data submitted, a shelf life was granted of 48 months. No specific storage conditions need to be included in the SmPC or on the label.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Certificates of suitability issued 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 MEB considers that Paracetamol PharmaMatch 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 PharmaMatch 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 Panadol, 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 MEB finds 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 MEB finds that no further clinical studies are required.

IV.2 Pharmacokinetics

Instead of conducting a bioequivalence study, the MAH has applied for a BSC (Biopharmaceutics Classification System)-based biowaiver. As described in the requirements of the EMA Guideline on Bioequivalence, this type of biowaiver is restricted to highly soluble drug substances with known human absorption and considered not to have a narrow therapeutic index. The concept is applicable to immediate release, solid pharmaceutical products for oral administration and systemic action, having the same pharmaceutical form.

The MAH has sufficiently shown that all criteria for a BCS-based biowaiver were met:

- Paracetamol has been proven to exhibit high solubility and complete absorption.
- 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. Dissolution data at a pH 1.2, 4.5 and 6.8 between

PharmaMatch and the reference product showed comparable and very rapid dissolution.

- 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 data supporting the BCS-class biowaiver is considered as sufficient and the biowaiver could be 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 PharmaMatch.

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

Important identified risks	-
Important potential risks	-
Missing information	-

The MEB finds 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 Panadol. No new clinical studies were conducted. The MAH demonstrated 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

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Kruidvat Paracetamol liquid caps 500 mg, soft capsules (NL RVG 116359) The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Paracetamol PharmaMatch 500 mg, oval, tablets has a proven chemical-pharmaceutical quality and is a generic form of Panadol glade tablet 500 mg, tablets. Panadol is a well-known medicinal product with an established favourable efficacy and safety profile.

A biowaiver was granted in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

The MEB, based on the data submitted, considered that essential similarity has been demonstrated for Paracetamol PharmaMatch 500 mg, oval, tablets with the reference product, and has therefore granted a marketing authorisation. The procedure was finalised with a positive outcome on 14 January 2022.

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
IB	Other variation	Yes	24-06-2022	Approved	N/A
IA	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability New certificate from a new manufacturer (replacement or addition)	No	25-07-2022	Approved	N/A