

Public Assessment Report

Scientific discussion

Paracetamol Pharmacin 1000 mg, tablets (paracetamol)

NL/H/2791/001/DC

Date: 22 April 2014

This module reflects the scientific discussion for the approval of Paracetamol Pharmacin 1000 mg, tablets. The procedure was finalised on 12 November 2013. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Paracetamol Pharmacin 1000 mg, tablets from Pharmacin B.V.

The product is indicated for treatment of mild to moderate pain and/or fever in adults and adolescents only.

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 Panadol 1000 mg tablets (NL License RVG 26161), which has been registered in the Netherlands by GlaxoSmithKline Consumer Healthcare B.V. since 11 December 2000. In addition, reference is made to Panadol authorisations in the individual member states (reference product)

The concerned member states (CMS) involved in this procedure were Portugal and Spain.

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

II. QUALITY ASPECTS

II.1 Introduction

Paracetamol Pharmacin 1000 mg is a white to off white biconvex oblong, uncoated tablets with break line on both sides. The tablet can be divided into equal doses.

The tablets are packed in PVC-Alu blister strips.

The excipients are: sodium starch glycolate (Type A Primogel), povidone K30 (E1201), pregelatinized maize starch, stearic acid (E570)

II.2 Drug Substance

The active substance is paracetamol, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a white crystalline powder, which is sparingly soluble in water, freely soluble in alcohol and very slightly soluble in methylene chloride. No polymorphs are reported in literature for paracetamol.

The CEP procedure is used for all three manufacturers of 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

CEPs have been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

Reference to the CEPs and the Ph.Eur. is made concerning the drug substance specifications. As compendial analytical methods are used, submission of validation data is not required. Batch analysis results on three batches have been included.

Stability of drug substance

For the first manufacturer, results of analysis of 3 batches kept under accelerated conditions show that the material is stable for 6 months. The long-term stability studies for 24 months show that the drug substance is stable and hence a re-test period of 2 years can be granted.

For the other two manufacturers, the re-test periods stated in the CEPs, 4 years and 5 years, are applied by the MAH as well.

II.3 Medicinal Product

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The MAH applied for a biowaiver and included comparative *in vitro* dissolution data to demonstrate the immediate release character of his product and to demonstrate similarity of the dissolution profiles with the reference product. Comparative dissolution profiles demonstrate that paracetamol 1000 mg tablets release more than 85% of the paracetamol within 10 minutes in all dissolution media tested. The MAH has justified the use of the UK reference product and has provided comparative dissolution profiles with the reference product sourced from the Netherlands. The assessment of the biowaiver is presented in the clinical part of this report. Data of the three validation batches demonstrated that the tablets comply with the requirements of the subdivision of tablets according the Ph. Eur Tablets monograph. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

A standard manufacturing process based on wet granulation is applied. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three pilot-scale batches. The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post authorization.

Control of excipients

All excipients used are controlled according to the specifications and analytical procedures of the corresponding monographs in the Ph.Eur. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for appearance, identity, assay, degradation, disintegration, dissolution, hardness, water content, friability, uniformity of dosage units, average weight, microbial purity and subdivision of tablets. The proposed specifications are acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three pilot-scale batches, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided for three pilot-scale batches stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the packaging proposed for marketing. No significant trends are seen and all results comply with the limits in the finished product specifications. Slight photosensitivity was noted. Based on the stability data, a shelf life of 36 months can be granted with storage condition 'keep blister in the outer carton in order to protect from light'.

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 Pharmacin 1000 mg tablets 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 Pharmacin 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 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

Biowaiver

Paracetamol is a long-standing drug and its safety/efficacy profile and use are well-established. A Biopharmaceutics Classification System (BCS) based biowaiver is applicable to paracetamol based on the following:

- Paracetamol 1000 mg tablets are immediate-release, solid pharmaceutical forms for oral administration and systemic action.
- Paracetamol is not a narrow therapeutic index drug
- Paracetamol is a BCS Class I drug, *i.e.* high permeability and high solubility
- The excipients used in the generic tablet formulation are partly comparable to the excipients used in the reference formulation. The other excipients are used in normal quantities and are considered not to affect bioavailability.
- The dissolution profile was demonstrated to be comparable to the reference product.

As similarity between the test and reference product has been adequately demonstrated, a BCS-based biowaiver can be accepted.

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 Pharmacin 1000 mg tablets.

Summary table of safety concerns as approved in RMP

Important identified risks	Hepatotoxicity/ abnormal liver function (Patients with pre-existing liver disease, chronic alcoholism, malnutrition, dehydration, underweight adults) Overdose (non-intentional and intentional) Interaction with anticoagulants Interaction with enzyme inducers
Important potential risks	Medication overuse headache
Important missing information	Off-label use (patients younger than 12 years of age, adolescents with small body weight) Medication errors

Routine pharmacovigilance is currently considered sufficient for paracetamol 1000 mg tablet formulations, as for the reference product no additional pharmacovigilance measures are in place.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Panadol 1000 mg tablets. No new clinical studies were conducted. No comparative bioavailability or bioequivalence study was carried out. Instead, reference was made to fulfilling all requirements for a biowaiver. This has been sufficiently demonstrated.

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. Section 1, 2, 4 and 5 of the submitted package leaflet are almost identical to the approved package leaflet of Paracetamol Accord 1000 mg effervescent tablets (procedure UK/H/1747/001/DC). Section 3 of the submitted package leaflet is in line with the PL of Hedavic 1000 mg, tablets (procedure NL/H/2098/001/DC). Furthermore, a tested layout is used. The bridging report submitted by the MAH has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Paracetamol Pharmacin 1000 mg, tablets has a proven chemical-pharmaceutical quality and is a generic form of Panadol 1000 mg. Panadol is a well-known medicinal product with an established favourable efficacy and safety profile. The prescription status for paracetamol is non prescription in all member states. In the Netherlands the prescription status for paracetamol 1000 mg is 'pharmacy only'.

No comparative bioavailability or bioequivalence study was carried out. A biowaiver is justified.

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 Pharmacin 1000 mg tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 12 November 2013.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached