COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Paracetamol liquid caps HTP 500 mg, soft capsules
(paracetamol)

NL/H/5111/001/DC

Date: 15 July 2021

This module reflects the scientific discussion for the approval of Paracetamol liquid caps HTP 500 mg, soft capsules. The procedure was finalised at 18 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 liquid caps HTP 500 mg, soft capsules, from Healthypharm B.V.

The product is indicated for the short-term treatment of headache, toothache, muscle ache, lumbago, fever and pain with flu and colds.
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 Zapp, film-coated tablets 500 mg (NL RVG 26469) which has been registered in The Netherlands by GlaxoSmithKline Consumer Healthcare B.V. since 5 August 2002.

The concerned member states (CMS) involved in this procedure were Ireland, Portugal and Slovakia.

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

II. QUALITY ASPECTS

II.1 Introduction

Paracetamol liquid caps HTP are white, opaque coloured, oval shaped, soft gelatin capsules containing off white to white colour suspension, imprinted with "P500" in black colour edible ink.

Each soft capsule contains as active substance 500 mg of paracetamol.

The soft capsules are packed in opaque PVC/PVDC-Al blisters.

Excipients of the capsule content are macrogol 400, propylene glycol (E 1520), colloidal hydrated silica and purified water. Excipients of the capsule shell are gelatin, sorbitol liquid (E 420), titanium dioxide and purified water. Other excipients are printing ink (Opacode black S-1-17823), shellac glaze 45% (20% esterified) in ethanol, black iron oxide and propylene glycol (E1520).

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, sparingly soluble in water, freely soluble in ethanol (96%) and very slightly soluble in methylene chloride. Paracetamol shows polymorphism. Polymorphic form I is consistently produced and stabile during the shelf life of the drug substance.

The CEP procedure is used for the active substance with a CEP. 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 of the drug product manufacturer is in line with the Ph.Eur. monograph for paracetamol and the CEP. The specification is considered acceptable.

Batch analytical data demonstrating compliance with the drug substance specification have been provided on three batches.

Stability of drug substance
The active substance is stable for 66 months (re-test period) when stored under the stated conditions. This aspect has been evaluated within the scope of the CEP procedure by the EDQM and the conclusion is taken from the CEP.

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 development was based on characteristics of the reference product Panadol Zapp of GlaxoSmithKline Consumer Healthcare B.V., other comparable drug products, the related quality target product profile and critical quality attributes, experience of the drug product manufacturer with the excipients and the drug substance characteristics. The compatibility of the drug substance with the proposed excipients has been extensively studied. A risk assessment and risk reduction tool was used.

The quality control dissolution method has been adequately established and is considered sufficiently discriminatory. Comparative dissolution studies were performed in line with the EMA Guideline on the investigation of bioequivalence with three different buffers (normally pH 1.2, 4.5 and 6.8) and the media intended for drug product release (QC media) with the batches of test product and reference product that were both used in the bioequivalence study. It has been adequately demonstrated that the comparative *in vitro* dissolution of the bio batches do not reflect similarity due to the different dosage forms, and the *in vivo* study results prevail. A commitment to perform comparative dissolution profile testing for the first three production scale batches has been provided.

Manufacturing process
The manufacturing process has been validated according to relevant European guidelines. The manufacturing process consists of ten phases: dispensing, medicament fill preparation, gelatin shell mass preparation, colour solution preparation, encapsulation, drying, polishing, printing, inspection and packaging. Process validation data on the product has been presented for three exhibit batches. Although the manufacturing process is a non-standard process the provided process validation is sufficient as the drug product manufacturer has experience with this type of manufacturing process, and the full scale process will be performed with the same equipment as for the validated scale.

Control of excipients
The excipients comply with Ph.Eur. requirements and 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 of paracetamol, uniformity of dosage units, dissolution, related substances, assay of paracetamol, loss on drying, length and width of capsules and microbial enumeration. The release and shelf life specification are identical. The specification is considered acceptable. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three exhibit batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product has been provided for three exhibit batches stored at 25°C/60%RH (30 months) and 40°C/75%RH (6 months). 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 36 months. The labelled storage conditions are “do not store above 30°C” and “store in the original package in order to protect from moisture”.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

The gelatin is sourced from bovine. Therefore, 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 liquid caps HTP have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made:

- To perform comparative dissolution profile testing for the first three production scale batches.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Paracetamol liquid caps HTP are 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 Zapp 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.

For this generic application, the MAH has submitted a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Paracetamol liquid caps HTP 500 mg, soft capsules (Healthypharm B.V., The Netherlands) is compared with the pharmacokinetic profile of the reference product Panadol Zapp, film-coated tablets 500 mg (GlaxoSmithKline Consumer Healthcare B.V.,The Netherlands).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of the reference product in different member states.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

<u>Bioequivalence study</u>
Design
A open-label, randomised, two-treatment, two-period, two-sequence, single oral dose, two-way crossover bioequivalence study was carried out under fasted conditions in 28 healthy male subjects, aged 19-44 years. Each subject received a single dose (500 mg) of one of the two active substance formulations. The tablet was orally administered with 240 ml water

after overnight fast of at least 10 hours. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected at one hour prior to the dosing and post-dose blood samples were drawn at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12 and 24 hours.

The design of the study is acceptable.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
One subject withdrew from the study on its own accord and one subjects was excluded due to a high pre-dose blood concentration. 26 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of paracetamol under fasted conditions.

Treatment N= 26	**AUC_{0-t}** (ng.h/ml)	**$AUC_{0-\infty}$** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)
Test	24.76 ± 7.15	26.19 ± 7.60	8.18 ± 2.51	0.75 (0.50 – 2.50)
Reference	24.62 ± 6.43	25.93 ± 6.86	8.27 ± 2.61	0.50 (0.50 – 2.00)
***Ratio (90% CI)**	1.02 (0.97 – 1.08)	1.03 (0.98 – 1.08)	1.02 (0.88 – 1.18)	-

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration

**ln-transformed values*

Conclusion on bioequivalence study
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Paracetamol liquid caps HTP are considered bioequivalent with Panadol Zapp.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

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 liquid caps HTP 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 Panadol Zapp. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study 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

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 3 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 liquid caps HTP 500 mg, soft capsules have proven chemical-pharmaceutical quality and is a generic form of Panadol Zapp, film-coated tablets 500 mg. Panadol Zapp 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 liquid caps HTP 500 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 18 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