CBG MEB

Public Assessment Report

Scientific discussion

Kruidvat Paracetamol liquid caps 500 mg, soft capsules

(paracetamol)

NL License RVG: 116359

Date: 10 April 2017

This module reflects the scientific discussion for the approval of Kruidvat Paracetamol liquid caps 500 mg. The marketing authorisation was granted on 12 May 2016. 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
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
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 Kruidvat Paracetamol liquid caps 500 mg, soft capsules from Marel B.V.

The product is indicated for headache, dental pain, muscular pain, lumbago, neuralgia, menstrual pain, fever and pain during influenza and common cold, fever and pain after vaccination.

A comprehensive description of the indications and posology is given in the SmPC.

This national procedure concerns a generic application. Panadol 500 mg, film-coated tablets, registered in France by GlaxoSmithKline (GSK) Santé Grande Public since 1996 is used as a European Reference Product. In the Netherlands Panadol Zapp 500 mg, film-coated tablets (NL License RVG 26469) has been authorised by GlaxoSmithKline Consumer Healthcare B.V. since 5 August 2002. No registration of Panadol soft capsules has been granted in the Netherlands.

According to the Guideline on the Investigation of Bioequivalence, various immediate-release oral pharmaceutical forms can be considered to be one and the same pharmaceutical form. Kruidvat Paracetamol liquid caps can therefore be treated as a generic medicinal product to reference Panadol 500 mg film-coated tablets.

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

II. QUALITY ASPECTS

II.1 Introduction

Kruidvat Paracetamol liquid caps 500 mg is a white, oblong (size 11) soft gelatin capsule containing 500 mg of paracetamol.

The capsules are packed in white PVC/PVdC-Al blisters.

The excipients are:
capsule content - macrogol 400, macrogol 600, purified water, propylene glycol, povidone, colloidal anhydrous silica
capsule shell – gelatin, partially dehydrated liquid sorbitol, purified water, glycerol, titanium dioxide (E171)
processing aids - medium chain triglycerides, soy lecithin

II.2 Drug Substance

The active substance is paracetamol, an established active substance described the European Pharmacopoeia (Ph.Eur.). The active substance is a white or almost white crystalline powder. It is sparingly soluble in water, freely soluble in alcohol and very slightly soluble in methylene chloride. It has been adequately demonstrated that polymorphic form I is manufactured.

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. and the additional tests of the CEP. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
The active substance is stable for 4 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. The objective was to develop a paracetamol 500 mg soft gelatin capsule comparable in clinical performance to Panadol 500 mg film-coated tablets marketed in France (the European reference product). Both products are immediate-release oral pharmaceutical forms that can be considered to be one and the same pharmaceutical form according to the Guideline.

One bioequivalence study was performed. From a quality point of view, the batches used in the bioequivalence study are acceptable. Differences in dissolution profiles are seen and equivalence can not be concluded based on the dissolution. However, in such a case the results from the bioequivalence study prevail over the dissolution data. Possible reasons for the discrepancy were addressed and are considered justified.

Manufacturing process
The excipients used for the capsule fill and drug substance are mixed, while a gel mass is prepared, this is followed by encapsulation, drying and packaging. The manufacturing process is described in sufficient detail. Although it concerns a specialised pharmaceutical dosage form, the manufacturing is seen as a standard process for this drug product manufacturer. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation for full-scale batches will be performed post authorisation.

Control of excipients
The excipients comply with their respective Ph.Eur. monographs or United States National Formulary (lecithin). 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, disintegration, identification, uniformity of dosage units, assay, dissolution, related substances and microbial contamination. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Release and shelf-life limits are the same. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from four 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 has been provided for three batches of the minimum batch size stored at 25°C/60% RH (24 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 proposed packaging. Photostability studies have been performed and results show that the product is not susceptible to light degradation. As results of dissolution testing are not shown to be within specification at accelerated conditions, the storage restriction of “do not store above 25°C” is currently required. However, the MAH has committed to perform studies at 40°C/75% RH and/or 30°C/65% RH in order to fully establish the storage restrictions. A shelf-life period of 24 months is granted.

Specific measures for the prevention of the transmission of animal spongiform encephalopathies
Gelatin is the only excipient of animal origin. Certificates of suitability issued by the EDQM have been provided demonstrating compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Kruidvat Paracetamol liquid caps 500 mg 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 Kruidvat Paracetamol liquid caps 500 mg 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 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 MEB agrees 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

Bioequivalence study
The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Kruidvat Paracetamol liquid caps 500 mg (Marel B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Panadol 500 mg, film-coated tablets (GlaxoSmithKline Santé Grande Public, France).

The choice of the reference product
The choice of the French reference product in the bioequivalence study is justified in view of the composition of the French and Dutch innovator products.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Design
An open-label, single-dose, randomised, two-treatment, two-period, two-sequence, cross-over bioequivalence study was carried out under fasted conditions in 32 healthy male (n=16) and female (n=16) subjects, aged 18-47 years. Each subject received a single dose (500 mg) of one of the two paracetamol formulations. The product was orally administered with 200 ml water after an overnight fast of at least 10 hours. Fasting was continued until 4 hours after dosing. There were 2 dosing periods, separated by a washout period of 5 days.

Blood samples were collected at pre-dose and 0.17, 0.25, 0.33, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 8, 10 and 12 hours after administration of the products.

The design of the study is acceptable. The wash-out period of 5 days is more than 5 half-lives of paracetamol (half-life of paracetamol is 1.9-4.3 hours). Furthermore, the sampling frequency around expected t_{max} of ~1 h is considered acceptable to adequately capture peak plasma concentrations. The sampling period was long enough to cover the absorption phase as the AUCt covered more that 80% of the $AUC_{0-\infty}$. Paracetamol may be taken regardless of food. Hence, a study under fasting conditions is appropriate as this is the most sensitive condition to detect difference between the test and reference products.

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
No subjects withdrew from the study and all 32 subjects were included in the statistical analysis.

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

Treatment N=32	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	19.3 ± 5.1	20.3 ± 5.4	7.4 ± 3.1	0.62 (0.25-2.5)
Reference	19.5 ± 4.7	20.5 ± 5.0	7.2 ± 2.2	0.54 (0.25-1.0)
***Ratio (90% CI)**	0.99 (0.96-1.02)	--	1.01 (0.93-1.10)	--
$AUC_{0-\infty}$ 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} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Kruidvat Paracetamol liquid caps is considered bioequivalent with Panadol 500 mg film-coated tablets.

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 Kruidvat Paracetamol liquid caps 500 mg, soft capsules.

- 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
Missing information	• Use in children <6 years of age (500 mg). • Medication errors.

The MEB 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. 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 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 2 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.
In both test rounds at least 90% of all participants were able to find the information. Of these participants, more than 90% were able to answer the question correctly. The results show that the package leaflet 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

Kruidvat Paracetamol liquid caps 500 mg, soft capsules has a proven chemical-pharmaceutical quality and is a generic form of Panadol 500 mg, film-coated tablets. Panadol 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.

The MEB, on the basis of the data submitted, considered that essential similarity with the reference product has been demonstrated, and have therefore granted a marketing authorisation. Kruidvat Paracetamol liquid caps 500 mg was authorised in the Netherlands on 12 May 2016.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Replacement of a release site and is added as primary and secondary packager.	IA/G	30-5-2016	28-6-2016	Approval	N
Transfer MAH and change in the name of the medicinal product.	MAH Transfer	3-6-2016	4-7-2016	Approval	N
Change in SmPC and PL.	IB	25-8-2016	31-8-2016	Approval	N