CBG MEB

Public Assessment Report

Scientific discussion

Paracaps 500 mg, soft capsules

(paracetamol)

NL/H/3484/001/DC

Date: 27 February 2017

This module reflects the scientific discussion for the approval of Paracaps 500 mg, soft capsules. The procedure was finalised on 30 June 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

CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
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
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 Paracaps 500 mg, soft capsules from Baggerman FarmaNet NV.

The product is indicated for 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 reference product Panadol 500 mg, film-coated tablets registered in France by GlaxoSmithKline (GSK) Sante Grande Public since 9 February 1996. As no registration of Panadol film-coated tablets containing paracetamol has been granted in the Netherlands, the French product is used as European Reference Product.

The concerned member states (CMS) involved in this procedure were Belgium, Czech Republic, Luxembourg, Poland and Slovak Republic.

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

II. QUALITY ASPECTS

II.1 Introduction

Paracaps is a white, oblong soft gelatin capsule containing 500 mg of paracetamol.

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

The excipients are:
Capsule content - macrogol 400, macrogol 600, purified water, propylene glycol (E 1520), povidone (E1201) and colloidal anhydrous silica (E 551)
Capsule wall – gelatin (E 441), partly dehydrated liquid sorbitol, purified water, glycerol (E 422) and titanium dioxide (E 171)
Trace substances - isopropyl alcohol, medium chain triglycerides and soya lecithin

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. 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 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 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. Paracaps 500 mg soft gelatin capsules can be treated as a generic medicinal product to reference Panadol 500 mg film coated tablets, as 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. Furthermore, the Paracaps capsules have the same active ingredient, are of the same strength, and are expected to have the same therapeutic effect as the reference product Panadol 500 mg film coated tablets.

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 concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM have been provided for the excipient gelatine 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 Paracaps 500 mg, soft capsules has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No non-standard post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Paracaps 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

Pharmacological, pharmacokinetic and toxicological characteristics of paracetamol as presented in the non-clinical overview, based on literature review, are considered appropriate. There are no issues relating to the pharmacology or toxicology and formulation of paracetamol. 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 one 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 Paracaps 500 mg, soft capsules (Baggerman FarmaNet NV., The Netherlands) is compared with the pharmacokinetic profile of the reference product Panadol 500 mg, film-coated tablets (GlaxoSmithKline Sante Grande Public, France).

The choice of the reference product
The choice of the French reference product in the bioequivalence study has been justified. 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. There were two dosing periods, separated by a washout period of 7 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. Paracetamol may be taken regardless of food. 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 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=32	**AUC_{0-t}** µg.h/ml	**$AUC_{0-\infty}$** µg.h/ml	**C_{max}** µg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	19.3 ± 5.1	20.3 ± 5.4	7.44 ± 3.1	0.50 (0.25 - 2.5)	2.75 ± 0.45
Reference	19.5 ± 4.7	20.5 ± 5.0	7.19 ± 2.2	0.50 (0.25 - 1.0)	2.89 ± 0.90
***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
$t_{1/2}$ half-life

**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 Paracaps 500 mg, soft capsules 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 Paracaps.

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 <9 years of age (500 mg) • Medication errors

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 film-coated tablets. 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

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 the same class of medicinal products. 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

Paracaps 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.

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 Paracaps with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 30 June 2016.

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
Art 61.3 notification to bring the PL in line with the SmPC. The amendment concerns the description of the product.	NL/H/3484/001/P/001	P	23-9-2016	13-10-2016	Approval	N