Public Assessment Report

Scientific discussion

Paracetamol Disphar 1000 mg, granules
(paracetamol)

NL License RVG: 113944

Date: 13 October 2016
## List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASMF</td>
<td>Active Substance Master File</td>
</tr>
<tr>
<td>CEP</td>
<td>Certificate of Suitability to the monographs of the European Pharmacopoeia</td>
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<tr>
<td>CHMP</td>
<td>Committee for Medicinal Products for Human Use</td>
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<tr>
<td>CMD(h)</td>
<td>Coordination group for Mutual recognition and Decentralised procedure for human medicinal products</td>
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<tr>
<td>CMS</td>
<td>Concerned Member State</td>
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<tr>
<td>EDMF</td>
<td>European Drug Master File</td>
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<tr>
<td>EDQM</td>
<td>European Directorate for the Quality of Medicines</td>
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<td>EEA</td>
<td>European Economic Area</td>
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<tr>
<td>ERA</td>
<td>Environmental Risk Assessment</td>
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<tr>
<td>ICH</td>
<td>International Conference of Harmonisation</td>
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<tr>
<td>ISR</td>
<td>Incurred Sample Reanalysis</td>
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<tr>
<td>MAH</td>
<td>Marketing Authorisation Holder</td>
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<tr>
<td>Ph.Eur.</td>
<td>European Pharmacopoeia</td>
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<td>PL</td>
<td>Package Leaflet</td>
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<td>RH</td>
<td>Relative Humidity</td>
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<tr>
<td>RMP</td>
<td>Risk Management Plan</td>
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<tr>
<td>SmPC</td>
<td>Summary of Product Characteristics</td>
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<tr>
<td>TSE</td>
<td>Transmissible Spongiform Encephalopathy</td>
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</table>
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 Disphar 1000 mg, granules from Disphar International B.V.

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 national procedure concerns a hybrid application with a change in pharmaceutical form and strength. Paracetamol Disphar 1000 mg is formulated as granules, whereas the reference product Panadol 500 mg is an immediate release tablet. The application is a line-extension of Paracetamol Disphar 500 mg, granules (NL License RVG 110486).

Oral paracetamol has been marketed in Europe for more than 50 years, mostly as conventional immediate release tablets containing 500 mg paracetamol. In the Netherlands, Panadol Gladde Tablet has been registered by GlaxoSmithKline Consumer Healthcare B.V. since 1995 (NL License RVG 18550). The product was first authorised in the Netherlands in 1956.

The marketing authorisation is granted based on article 10(3) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Paracetamol Disphar 1000 mg is a white to off-white, freely flowable granulate.

The granules are packed in PETP/Alu/PE sachets.

The excipients are: basic butylated methacrylate copolymer, colloidal hydrated silica, stearic acid, sodium laurilsulfate, xylitol (E967), saccharin sodium (E954), aspartame (E951), grapefruit flavour (containing potato maltodextrin, acacia gum (E 414), butylhydroxyanisol (E 320)).

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, which is sparingly soluble in water. Paracetamol does not have chiral centra and exists as three polymorphic forms. One polymorphic form is used.

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 drug substance specification is in line with the Ph.Eur and the CEP, with additional requirements for particle size. The specification is acceptable in view of various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full-scale batches.
Stability of drug substance
The active substance is stable for 5 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 development of the product has been described, the choice of excipients is justified and their functions explained. The objective was to develop a very rapid dissolution profile with acceptable organoleptic characteristics. The optimal granular grade of paracetamol was established. The dissolution profile of drug product obtained with varying percentages of coating was measured at various pH values. The dissolution profile of Paracetamol Disphar granulate was compared to Panadol 500 mg tablets. The manufacturing process of the 500 mg and 1000 mg granules is identical. The only difference between these two finished product strengths is the mass of granules filled in the stick packs. Therefore, it is not deemed necessary to provide additional dissolution data on the 1000 mg sticks. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing consists of four production steps: microencapsulation of paracetamol, mixing blend 1, mixing blend 2, preparing the final blend (granules) and packaging. The manufacturing process is considered a non-standard process due to the microencapsulation process. The manufacturing process has been adequately validated according to relevant European guidelines.

Control of excipients
The excipients comply with the Ph.Eur. and adequate in-house specifications. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identity, assay, dissolution, degradation, moisture, uniformity of dosage units and microbial purity. The shelf-life requirements are identical to the release specification. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on two validation batches at commercial scale, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product have been provided for the two commercial-scaled validation batches of the 1000 mg strength stored at 25°C/60% RH (6 months) and 40°C/75% RH (6 months). Stability results of the 500 mg sticks are used as supportive data. Results of two batches of the 500 mg sticks stored at 25°C/60% RH (24 months), 30°C/75% RH (24 months) and 40°C/75% RH (6 months). The conditions used for the commercial packaging in the stability studies are according to the ICH stability guideline.
The results over the limited period do not show out-of-specifications or significant trends. Based on the available stability data on the 500 mg and 1000 mg granules, a shelf life of 3 years has been granted. No specific storage condition is required. The packaging material is a high barrier laminate against moisture, light and oxygen.

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 MEB considers that Paracetamol 1000 mg granules 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 Disphar is intended as a substitute for other identical products on the market, 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 hybrid 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.

IV.2 Pharmacokinetics

The MAH discussed the possibility for a bioequivalence study for this hybrid application. In the bioequivalence study the pharmacokinetic profile of the test product Paracetamol Disphar 500 mg, granules (Disphar International B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Panadol 500 mg film-coated tablets (GlaxoSmithKline Consumer Healthcare B.V., the Netherlands).

Two single-dose packs of the 500 mg granules were used in the study. This is acceptable as the manufacturing process of the 500 mg and 1000 mg granules is identical. The only difference is the mass of granules filled in the stick packs. The choice of the reference product in the bioequivalence study has been justified.

Bioequivalence studies

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 26 healthy subjects (13 males/13 females), aged 19-48 years.
Just before test product administration the subjects received and swallowed 20 mL of water to wet the mouth. The medication (1000 mg, 2 x 500 mg granules of the test product or two 500 mg tablets of the reference product) was administered orally to each subject. The test product was administered at the back of the tongue and swallowed without water while the reference product was administered with 200 mL of water. Immediately after administration, the subject's oral cavity and hands were checked to confirm complete medication and fluid intake. Two hours after dosing the subjects were allowed to drink 200 ml and breakfast was used 4 hours upon dosing.
There were 2 dosing periods, separated by a washout period of 5 days.

Blood samples were collected pre-dose and at 0.08, 0.17, 0.33, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.0, 3, 4, 6, 8, 12, 16, and 24 hours after administration of the products.
The overall study design is considered acceptable considering the absorption rate and half-life. Also the washout period is acceptable. As this product can be taken regardless food intake, a study under fasting conditions is justified.

**Analytical/statistical methods**

An Incurred Sample Reanalysis (ISR) was not performed as required by the current guideline on bioanalytical methods. The MAH submitted the ISR from another bioequivalence study for paracetamol, which meets the requirements in the Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009). This other study used the same extraction and separation methods used in the study for Paracetamol Disphar granulate. The analytical method is considered the same except for the use of a different internal standard, which is more appropriate for the determination of paracetamol, and a lower validation range, which is acceptable as the concentrations measured in the ISR samples are within this range. The results of the different validation parameters for both original and modified method are comparable and the data for ISR generated with the re-validated method is considered acceptable. Overall, the validity of the analytical method is considered sufficiently demonstrated.

**Results**

One subject was withdrawn before the second period due to adverse event (tonsillitis). The remaining 25 subjects completed the study and were eligible for pharmacokinetic analysis.

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N=25</th>
<th>AUC\text{0-4} µg.h/ml</th>
<th>AUC\text{0-∞} µg.h/ml</th>
<th>C\text{max} µg/ml</th>
<th>t\text{max} h</th>
<th>t\text{1/2} h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>51.9 ± 13.8</td>
<td>52.9 ± 14.2</td>
<td>14.3 ± 5.12</td>
<td>1.0 (0.33-2.0)</td>
<td>4.4 ± 1.5</td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>50.3 ± 12.8</td>
<td>51.1 ± 13.3</td>
<td>16.1 ± 6.31</td>
<td>0.5 (0.33-2.0)</td>
<td>4.2 ± 1.3</td>
<td></td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>1.03 (0.99 – 1.07)</td>
<td>--</td>
<td>0.90 (0.81 – 1.00)</td>
<td>--</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV (%)</td>
<td>9.0</td>
<td>--</td>
<td>21.7</td>
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<td></td>
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</tr>
</tbody>
</table>

*ln-transformed values

**Conclusion on bioequivalence study**

The 90% confidence intervals calculated for AUC\text{0-4} and C\text{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Paracetamol Disphar 500 mg granules 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 Paracetamol Disphar.
## 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 with Paracetamol Disphar 500 mg granules that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference product.

## V. USER CONSULTATION

The package leaflet has not been evaluated via a user consultation study. The MAH uses a bridging approach. Reference is made to the successfully user tested PL for Paracetamol Disphar 500 mg granules. The bridging report has been found acceptable. Additional user testing is not required.

## VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Paracetamol Disphar 1000 mg, granules has a proven chemical-pharmaceutical quality and is a hybrid 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 MEB, on the basis of the data submitted, considered that similarity has been demonstrated for this hybrid formulation with the reference product, and has therefore granted a marketing authorisation. Paracetamol Disphar 1000 mg, granules was authorised in the Netherlands on 23 September 2014.
### STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Scope</th>
<th>Type of modification</th>
<th>Date of start of the procedure</th>
<th>Date of end of the procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implementation of the wording agreed by the competent authority (PRAC – Ref. no. EMA/PRAC/65788/2014) and QRD guidelines.</td>
<td>IB</td>
<td>31-3-2015</td>
<td>22-5-2015</td>
<td>Approval</td>
<td>N</td>
</tr>
</tbody>
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