Public Assessment Report

Decentralised Procedure

PARACETAMOL 1000 MG TABLETS

Procedure No: UK/H/5004/01/DC

UK Licence No: PL 18866/0060

Rockspring Healthcare Ltd
LAY SUMMARY

On 17 January 2013 the Medicines and Healthcare products Regulatory Agency (MHRA) granted a Marketing Authorisation to Rockspring Healthcare Ltd for the medicinal product Paracetamol 1000 mg Tablets (PL 18866/0060; UK/H/5004/01/DC). This medicine is only available on prescription from your doctor.

Paracetamol belongs to a group of medicines called analgesics (painkillers) which also help to reduce your temperature when you have a fever.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Paracetamol 1000 mg Tablets outweigh the risks, hence, a Marketing Authorisation was granted.
TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Module</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Module 1: Information about initial procedure</td>
<td>4</td>
</tr>
<tr>
<td>Module 2: Summary of Product Characteristics</td>
<td>5</td>
</tr>
<tr>
<td>Module 3: Patient Information Leaflet</td>
<td>6</td>
</tr>
<tr>
<td>Module 4: Labelling</td>
<td>7</td>
</tr>
<tr>
<td>Module 5: Scientific Discussion</td>
<td>8</td>
</tr>
<tr>
<td>I Introduction</td>
<td></td>
</tr>
<tr>
<td>II About the product</td>
<td></td>
</tr>
<tr>
<td>III Scientific overview and discussion</td>
<td></td>
</tr>
<tr>
<td>III.1 Quality aspects</td>
<td></td>
</tr>
<tr>
<td>III.2 Non-clinical aspects</td>
<td></td>
</tr>
<tr>
<td>III.3 Clinical aspects</td>
<td></td>
</tr>
<tr>
<td>IV Overall conclusion and benefit/risk assessment</td>
<td></td>
</tr>
<tr>
<td>Module 6: Steps taken after initial procedure</td>
<td>15</td>
</tr>
</tbody>
</table>
Module 1
Information about the initial procedure

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Paracetamol 1000 mg Tablets</th>
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<td>Type of Application</td>
<td>Hybrid, Article 10(3)</td>
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<td>Active Substance</td>
<td>Paracetamol</td>
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<td>Form</td>
<td>Tablets</td>
</tr>
<tr>
<td>Strength</td>
<td>1000 mg</td>
</tr>
<tr>
<td>MA Holder</td>
<td>Rockspring Healthcare Ltd</td>
</tr>
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<td></td>
<td>38/40 Chamberlayne Road</td>
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<td></td>
<td>London NW10 3JE</td>
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<td></td>
<td>United Kingdom</td>
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<tr>
<td>Reference Member State (RMS)</td>
<td>UK</td>
</tr>
<tr>
<td>Concerned Member States (CMS)</td>
<td>AT, BG, CZ, EL, HU, IE, PL, RO, SK</td>
</tr>
<tr>
<td>Procedure Number</td>
<td>UK/H/5004/01/DC</td>
</tr>
<tr>
<td>Timetable</td>
<td>Day 210 – 7 November 2012</td>
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</tbody>
</table>
Module 2
Summary of Product Characteristics

In accordance with Directive 2010/84/EU, the Summaries of Product Characteristics (SmPCs) for products granted Marketing Authorisations at a national level are available on the MHRA website.
Module 3
Patient Information Leaflet

In accordance with Directive 2010/84/EU, the Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.
Module 4
Labelling

Product labelling pending
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the member states considered that the application for Paracetamol 1000 mg Tablets (PL 18866/0060; UK/H/5004/01/DC could be approved. This is a prescription-only medicine (POM) indicated for the symptomatic treatment of mild to moderate pain (such as headache, migraine, toothache, sore throat, backache, muscle pain, rheumatic pain, dysmenorrhoea) and/or fever in adults and adolescents aged 16 years and over, whose body weight is greater than 50 Kg.

This application was submitted via the Decentralised Procedure, with the UK as Reference Member State (RMS), and Austria, Bulgaria, Czech Republic, Greece, Hungary, Ireland, Poland, Romania and Slovakia as Concerned Member States (CMS).

This application was made under the Decentralised Procedure (DCP), according to Article 10(3) of Directive 2001/83/EC, as amended, cross-referring to Tachipirina 500mg paracetamol tablets by Aziende Chimiche Riunite Angelini Francesco A.C.R.A.F. SpA, which was granted Marketing Authorisation MA 012745 in Italy on 11 February 1978. The reference product has been authorised in the EEA for at least 10 years, therefore, the legal basis of this application is acceptable.

The analgesic effect of paracetamol is ascribable to a direct action, probably mediated by the opioid and serotoninergic system, on the central nervous system and to inhibition of the prostaglandin synthesis on a central level. In addition, paracetamol has a marked antipyretic activity.

A bioequivalence study was performed, comparing the pharmacokinetics of one Paracetamol 1000 mg Tablet (test product) and two reference products Tachipirana and Dafalgan in healthy subjects under single-dose fasted conditions. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence study, no new non-clinical or clinical data were submitted, which is acceptable given that the application was based on Paracetamol 1000 mg Tablets being a new strength of an originator product that has been in clinical use for over 10 years.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of this product. For manufacturing sites within the community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites. For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates, satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.
The RMS and CMS considered that the application could be approved at the end of procedure (Day 210) on 7 November 2012. After a subsequent national phase, a Marketing Authorisation was granted in the UK on 17 January 2013.

II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Paracetamol 1000 mg Tablets</th>
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<tbody>
<tr>
<td>Name of the active substance(s) (INN)</td>
<td>Paracetamol</td>
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<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Analgesics and antipyretics, anilides (N02BE01)</td>
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<td>Pharmaceutical form and strength(s)</td>
<td>Tablet; 1000 mg</td>
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<tr>
<td>Reference number for the Mutual Recognition Procedure</td>
<td>UK/H/5004/01/DC</td>
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<tr>
<td>Reference Member State (RMS)</td>
<td>United Kingdom</td>
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<tr>
<td>Concerned Member States (CMS)</td>
<td>AT, BG, CZ, EL, HU, IE, PL, RO, SK</td>
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<td>Marketing Authorisation Number</td>
<td>PL 18866/0060</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Rockspring Healthcare Ltd 38/40 Chamberlayne Road London NW10 3JE United Kingdom</td>
</tr>
</tbody>
</table>

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

DRUG SUBSTANCE

INN: Paracetamol
Chemical name: N-(4-hydroxyphenyl)acetamide
Structure:

![Structure diagram]

Molecular formula: C₈H₉NO₂
Molecular mass: 151.2
Appearance: White crystalline powder.
Solubility: Sparingly soluble in water, free soluble in alcohol and very slightly soluble in dichloromethane.

All aspects of the manufacture and control of the drug substance paracetamol are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

Appropriate stability data have been generated to support a suitable retest period for the active substance when stored in the proposed packaging.
DRUG PRODUCTS

Description and Composition
The tablets are white to slightly yellow and oblong in shape, with a smooth surface and central break line. Each tablet contains 1000 mg of paracetamol and the pharmaceutical excipients microcrystalline cellulose, carmelllose sodium low-substituted, Povidone K30, Povidone K90, magnesium stearate and silicone dioxide. Appropriate justifications for the inclusion of each excipient have been provided.

All excipients comply with their respective European Pharmacopoeia monographs, with the exception of silicone dioxide, which is controlled in line with the USP-NF monograph. In the absence of a European Pharmacopoeia monograph for this excipient this is satisfactory. Satisfactory Certificates of Analysis have been provided for all excipients, showing compliance with the proposed specifications.

None of the excipients contain materials of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

Pharmaceutical Development
The objective of the development programme was to formulate a safe, efficacious tablet that is bioequivalent to two tablets of the 500mg reference product, Tachipirina 500mg paracetamol tablets, and equivalent in terms of overall exposure to the 1g effervescent paracetamol formulation, Dafalgan 1000mg paracetamol effervescent tablets. Suitable pharmaceutical development data have been provided for this application.

Comparative in-vitro dissolution profiles have been provided for batches of the test product and appropriate reference products. The dissolution and impurity profiles were satisfactory.

Manufacturing Process
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. Based on production-scale batches, the manufacturing process has been validated using production-scale batches and has shown satisfactory results.

Control of Finished Product
The finished product specification is satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Container-Closure System
The tablets are packaged in opaque blisters made up of polyvinylchloride (PVC) thermoformed with an aluminium sheet coated with thermoforming film for polyvinylchloride (PVC). Pack sizes of 6 or 8 tablets (packed in one blister) or 12 or 16 tablets (packed in two blisters) are authorised, although not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging. All primary packaging complies with the European Pharmacopoeia and relevant regulations regarding use of materials in contact with food.
Stability of the product
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 4 years.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and, Labelling
The SmPC, PIL and labelling text are acceptable from a pharmaceutical perspective. The Marketing Authorisation Holder has committed to submitting mock-ups to the relevant competent authorities for approval before marketing any pack size.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (‘user testing’), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that patients/users are able to act upon the information that it contains.

MAA (Marketing Authorisation Application) form
The MAA form is satisfactory.

Expert report (Quality Overall Summary)
The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
The grant of a Marketing Authorisation is recommended.

III.2 NON-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of paracetamol are well-known, no new non-clinical data have been submitted and none are required.

The applicant’s non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the drug’s non-clinical pharmacology, pharmacokinetics and toxicology.

Suitable justification has been provided for non-submission of an Environmental Risk Assessment As this product is intended to be used in place of products that are currently marketed, no increase in environmental burden is anticipated.

The grant of a Marketing Authorisation is recommended.

III.3 CLINICAL ASPECTS
The clinical pharmacology of paracetamol is well-known. With the exception of data from the bioequivalence study described below, no new pharmacodynamic or pharmacokinetic data are provided or are required for this application.

Bioequivalence
A three-treatment, six-sequence, three-period, randomized, balanced, cross-over bioequivalence study with wash-out was conducted. The study duration in each subject was 31 days. Blood was drawn before dosing and at intervals up to 24 hours post-dosing. Subjects were dosed under fasting conditions, starting from 12 hours before until 4 hours post-dosing.
In addition, no liquids intake was allowed from 1 hour before until 2 hours post-dosing, apart from the water needed for drug administration. The treatments were administered in three randomized periods separated by a gap of 7 days for wash-out.

**Test and Reference Products**
The test product Paracetamol 1000 mg Tablets was compared with the reference products Tachipirina 500mg paracetamol tablets (x2) and Dafalgan 1000mg paracetamol effervescent tablets.

**Population Studied**
18 subjects were enrolled in the study and all completed. All data were used in the pharmacokinetic analysis and no significant protocol deviations took place.

**Analytical Methods**
The quantitation limit of the HPLC assay used was 0.2µg/ml. The validated range for the assay was 0.2µg/ml to 40µg/ml. The method is validated and well recognised.

**Pharmacokinetic Variables**
- Pharmacokinetic parameters: $C_{\text{max}}$, $AUC_{0-t}$ and $AUC_{0-\text{inf}}$, $t_{1/2}$
- Adverse events
- Laboratory tests (pre- and post-study)
- Vital signs (pre- and post-study)

**Statistical methods**
- Descriptive statistics
- Crossover ANOVA
- 90% confidence intervals
- two-one sided t test according to Schuirmann
- Wilcoxon signed rank test

An acceptance range for $C_{\text{max}}$, $AUC_{0-t}$ and $AUC_{0-\text{inf}}$ was set at 80-125% (log transformed)

**Results**
ANOVA for crossover trials did not show any significant effect. 90% confidence intervals on log10-transformed parameters were as follows:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>$T$ vs $R_1$</th>
<th>$T$ vs $R_2$</th>
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<tbody>
<tr>
<td></td>
<td>Geom Mean $T$</td>
<td>Geom Mean $R_1$</td>
</tr>
<tr>
<td>$C_{\text{max}}$</td>
<td>15.7</td>
<td>15.2</td>
</tr>
<tr>
<td>$AUC_t$</td>
<td>44.5</td>
<td>43.3</td>
</tr>
<tr>
<td>$AUC_\infty$</td>
<td>45.5</td>
<td>44.4</td>
</tr>
</tbody>
</table>

All subjects showed absence of drug levels prior to dosing for each period. The individual concentration/time curves show no unexpected results.

**Conclusion**
The applicant’s formulation showed bioequivalence to the two Tachipirina 500mg paracetamol tablets. It also showed equivalent overall exposure in the AUC results to the reference effervescent formulation, Dafalgan 1000mg paracetamol effervescent tablets, but a lower $C_{\text{max}}$ and longer $T_{\text{max}}$. 
EFFICACY
The efficacy of paracetamol is well-known. No new efficacy data have been submitted and none are required for this type of application.

SAFETY
With the exception of the data generated during the bioequivalence study no new safety data were submitted and none were required for this application. No new or unexpected safety issues were raised by the bioequivalence data.

PHARMACOVIGILANCE SYSTEM AND RISK MANAGEMENT PLAN
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Suitable justification has been provided for not submitting a Risk Management Plan for this product.

SUMMARY OF PRODUCT CHARACTERISTICS (SMPC), PRODUCT INFORMATION LEAFLET (PIL), LABELS
The SmPC, PIL and labels are acceptable from a clinical perspective. The SmPC is consistent with that for the reference product. The PIL is consistent with the details in the SmPC and is in line with the current guidelines. The labelling is in line with the current guidelines.

CLINICAL OVERVIEW
The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

CONCLUSION
The grant of a Marketing Authorisation is recommended.
IV OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Paracetamol 1000 mg Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted. As the pharmacokinetics, pharmacodynamics and toxicology of paracetamol are well-known, no additional data were required.

EFFICACY
With the exception of the bioequivalence study, no new data were submitted and none are required for applications of this type.

The applicant’s formulation showed bioequivalence to the two Tachipirina 500mg paracetamol tablets. It also showed equivalent overall exposure in the AUC results to the reference effervescent formulation, Dafalgan 1000mg paracetamol effervescent tablets, but a lower $C_{\text{max}}$ and longer $T_{\text{max}}$.

SAFETY
With the exception of the bioequivalence studies, no new data were submitted and none are required for applications of this type. As the safety profile of paracetamol is well known, no additional data were required. No new or unexpected safety concerns arose from the bioequivalence study.

PRODUCT LITERATURE
The SmPC, PIL and labelling are satisfactory and consistent with those for the reference product, where appropriate, and consistent with current guidelines.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with paracetamol is considered to have demonstrated the therapeutic value of the product. The benefit/risk balance is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE

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<th>Outcome</th>
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