IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Paracetamol & Caffeine 500 mg & 65 mg Tablets
Paracetamol
Caffeine
PA1186/026/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

I INTRODUCTION
This product was initially authorised under procedure number UK/H/4779/1/DC with the UK as RMS. The responsibility of RMS was transferred to Ireland on 14/01/2019 under procedure number IE/H/0904/1/DC.
Please note the following detail for the product in IE:
Marketing Authorisation Number: PA1186/026/001
Marketing Authorisation Holder: Chefaro Ireland DAC

The current Summary of Product Characteristics (SmPC) for this medicinal product is available on the HPRA website at www.hpra.ie.

The UK public assessment report published at the time of the initial marketing authorisation is provided herein.

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the member states considered that the application for Paracetamol and Caffeine, 500mg/65mg Tablets (PL 16028/0158; UK/H/4779/001/DC) could be approved. The application was submitted via the Decentralised Procedure, with the UK as Reference Member State (RMS), and Italy, Poland, Germany, Sweden, France, Norway, the Netherlands, the Czech Republic, Denmark, Finland, Hungary, Ireland and the Slovak Republic as Concerned Member States (CMS).

This product is not subject to medical prescription, but will be supplied through pharmacies only (legal status P).

This was an application made under the Decentralised Procedure (DCP), according to Article 10(1) of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of Panadol Extra Tablets (Smithkline Beecham (SWG) Limited), which was initially granted a marketing authorisation in the UK on 26 May 1988.

This product is indicated for the symptomatic treatment of mild to moderate pain and/or fever in adults and children aged 15 years or over.

Paracetamol has antipyretic and mild analgesic properties together with some anti-inflammatory activity. It may act predominantly by inhibiting prostaglandin synthesis in the central nervous system (CNS) and to a lesser extent through a peripheral action by blocking pain-impulse generation. It probably produces antipyresis by acting centrally on the hypothalamic heat-regulating centre to produce peripheral vasodilation, resulting in increased blood flow through the skin, sweating and heat loss. Caffeine is widely used as a CNS stimulant and is also considered to act as an adjunct to analgesics. It constricts cerebral vasculature and decreases cerebral blood flow and oxygen tension in the brain. It is believed that caffeine helps to relieve headache by providing a more rapid onset of action and/or enhanced pain relief with lower doses of analgesic.

No new clinical or non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

No bioequivalence or bioavailability studies have been performed in support of this application.
A biowaiver for not performing bioequivalence studies was submitted and is considered acceptable.

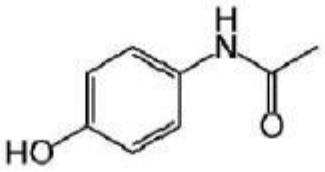
The RMS has been assured that acceptable standards of Good Manufacturing Practice are in place for this product type at all sites responsible for the manufacture, assembly and batch release of this product.

The RMS and CMS considered that the application could be approved with the end of procedure on 20 February 2013. After a subsequent national phase, a licence was granted in the UK on 24 April 2013.

II. QUALITY ASPECTS

S. Active substances – Paracetamol and Caffeine

rINN: Paracetamol
Chemical name: *N*-(4-hydroxyphenyl)ethanamide
Structure:



Molecular formula: $C_8H_9NO_2$
Molecular weight: 151.17
Appearance: White or almost white crystalline powder or colourless crystals, which is sparingly soluble in water, freely soluble in alcohol, very slightly soluble in methylene chloride.

rINN: Caffeine
Chemical name: 1,3,7-trimethyl-1H-purine-2,6(*3H,7H*)-dione
Structure:

Molecular formula: $C_8H_{10}N_4O_2$
Molecular weight: 194.2
Appearance: White or almost white crystalline powder or silky white or almost white crystals, which is sparingly soluble in water, freely soluble in boiling water, slightly soluble in ethanol (96%).

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

P. Medicinal Product

Other Ingredients

Other ingredients consist of the pharmaceutical excipients, namely maize starch, pregelatinised maize starch, povidone, stearic acid and talc.

All excipients comply with their respective European Pharmacopoeia monograph.

None of the excipients are sourced from animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of this product.

Pharmaceutical Development
The objective of the development programme was to formulate a globally acceptable, stable and bioequivalent product that could be considered a generic medicinal product of the innovator product, Panadol Extra Tablets (Smithkline Beecham (SWG) Limited).

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution and impurity profiles have been provided for the proposed product and its respective innovator product.

Manufacturing Process
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. Suitable in-process controls are in place to ensure the quality of the finished product.

Suitable validation data have been provided for pilot-scale batches produced by the finished product manufacturer. The applicant has committed to providing validation data from commercial-scale batches when these are available.

Finished Product Specification
The finished product specification proposed is acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for all working standards used.

Container-Closure System
The finished product is packaged in polyvinylchloride/aluminium blisters, which are packed into cardboard cartons in pack sizes of 10, 12, 20, 24 or 30 tablets. The marketing authorisation holder has stated that not all pack sizes are intended for marketing. However, they have committed to providing the relevant licensing authority with the mock-ups for any pack size before marketing it in that country.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

Stability of the product
Stability studies were performed on pilot-scale batches in accordance with current guidelines on batches of finished product manufactured by the finished product manufacturer and packed in the packaging proposed for marketing. The results from these studies support a shelf-life of 12 months, with the storage conditions "Do not store above 25°C. Keep the blister in the outer carton in order to protect from light." The applicant has committed to submitting stability results from commercial-scale batches as soon as these become available.

Bioequivalence/bioavailability
No bioequivalence or bioavailability studies have been performed in support of this application.
A biowaiver for not performing bioequivalence studies was submitted and is considered acceptable.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPC, PIL and labels are pharmaceutically acceptable.

A bridging report referring to the results of consultations with target patient groups ('user testing'), in accordance with Article 59 of Council Directive 2001/83/EC (as amended) for the package leaflet for the product Paracetamol Plus Caplets (PL 12063/0007) was provided. 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 the patients/users are able to act upon the information that it contains.

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

Quality Overall Summary (Expert report)
The pharmaceutical expert report 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. NON-CLINICAL ASPECTS

III.2 NON-CLINICAL ASPECTS

As the pharmacodynamic, pharmacokinetic and toxicological properties of paracetamol and caffeine are well-known, no further non-clinical studies are required and none have been provided.

The applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product's pharmacology and toxicology.

Suitable justification has been provided for the non-submission of an environmental risk assessment. As this product is intended for generic substitution with products that are currently marketed, no increase in environmental burden is expected.

There are no objections to the approval of this product from a non-clinical viewpoint.

IV. CLINICAL ASPECTS

III.3 CLINICAL ASPECTS

Pharmacokinetics

No bioequivalence or bioavailability studies have been performed in support of this application.
A biowaiver for not performing bioequivalence studies was submitted and is considered acceptable.
Both paracetamol and caffeine are highly soluble, with linear dose-dependent kinetics and the comparative dissolution curves are consistently equivalent over the appropriate pH range.

Efficacy

No new efficacy data have been submitted and none are required for this type of application.

Safety

No new safety data were submitted and none are required.

SmPC, PIL and Labels

The SmPC, PIL and labels are medically acceptable. The SmPC is consistent with that for the originator product.

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.

Clinical Expert Report

The clinical expert report 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.

V. OVERALL CONCLUSIONS

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Paracetamol and Caffeine, 500mg/65mg 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 and none are required for applications of this type.

CLINICAL

No new clinical data were submitted. A biowaiver for not performing bioequivalence studies was submitted and is considered acceptable.

No new or unexpected safety concerns arose from this application.

The SmPC, PIL and labelling are satisfactory and consistent with those for the reference product.

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 and caffeine is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.

VI. REVISION DATE

22/02/2022

VII. UPDATES

This section reflects the significant changes following finalisation of the initial procedure.

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
RMS transfer	From UK/H/4779/1/DC to IE/H/0904/1/DC			