IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Paralief Extra Film-coated Tablets Paracetamol 500 mg Caffeine 65 mg
Paracetamol
Caffeine
PA0126/337/001

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.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation on for Paralief Extra film coated tablets, from Chanelle Medical on 1st June 2018 for the symptomatic treatment of mild to moderate pain and /or fever in adults, the elderly and children aged 12 years and over.

The legal basis for this application for a Marketing Authorisation for Paralief Extra film coated tablets is a generic application according to Article 10(1) of the Directive 2001/83 EC as amended. The reference medicinal product is Panadol Extra film-coated tablets (PA0678/027/001) authorised in Ireland since 14/06/1994. The two products have the same qualitative and quantitative composition in terms of active substances and both are presented as tablet formulations.
The RMS is Ireland (IE) and the CMS' are ES, FR, HR, PL and IS.
No bioequivalence study has been performed and none is required as a BCS-based biowaiver is applicable to this medicinal product in accordance with Appendix III of CPMP/EWP/QWP/1401/98 Rev. 1/ Corr.
This is a non-prescription medicine which may be supplied through general sales.
The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie.

Name of the product: Paralief Extra film coated tablet
Name(s) of the active substance(s) (INN): Paracetamol /Caffeine
Pharmacotherapeutic classification (ATC code): NO2BE51 paracetamol, combinations excl. psycholeptics
Pharmaceutical form and strength(s): 500/65 mg film coated tablet
Marketing Authorisation Number(s) in Ireland (PA): PA0688/050/001
Marketing Authorisation Holder: Chanelle Medical (ES FR HR PL UK)
Day Zero (IS)
MRP/DCP No. : IE/H/478/001/DC
Reference Member State: IE
Concerned Member State: ES FR HR IS PL

II. QUALITY ASPECTS

II.1. Introduction
This application is for Paralief Extra film coated tablets.

II.2 Drug substance
The active substance is Paracetamol and Caffeine, an established active substance described in the European Pharmacopoeia and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)
The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product
P.1 Composition
Contains Paracetamol 500 mg and Caffeine 65 mg.
The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.
P.2 Pharmaceutical Development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.
P.3 Manufacture of the Product
The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.
The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.
P.4 Control of Other Substances (Excipients/*Ancillary Substances*)
All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.
P.5 Control of Finished Product
The Finished Product Specification is based on the pharmacopoeial monograph for tablets, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.
Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.
P.6 Packaging material
The approved packaging for this product is described in section 6.5 of the SmPC.
Evidence has been provided that the packaging complies with EU legislation for use with foodstuffs requirements.
P.7 Stability of the Finished Product
Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Paralief Extra film coated tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Panadol Extra film-coated tablets (PA0678/027/001) which has been on the European market for more than 15 years. No new preclinical data have been submitted. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application.

IV. CLINICAL ASPECTS

IV.1 Introduction

Paracetamol and caffeine are well-known active substances with established efficacy and tolerability.
Paracetamol is an analgesic and antipyretic agent with a usual adult dose of 500-1000mg.
Caffeine is a methylated xanthine and potent stimulant of the central nervous system. It is a widely used neurostimulant, being present in coffee, tea, soft drinks, chocolate, analgesics, and dietary supplements. Caffeine is frequently included in oral analgesic preparations at unit doses ranging from about 15 to 65mg.
The legal basis for this application for a Marketing Authorisation for Paralief Extra film coated tablets is a generic application according to Article 10(1) of the Directive 2001/83 EC as amended. The reference medicinal product is Panadol Extra film-coated tablets (PA0678/027/001) authorised in Ireland since 14/06/1994. The Marketing Authorisation Holder (MAH) for the reference medicinal product is Glaxo Smith Kline Consumer Health Care (Ireland) Ltd. The two products have the same qualitative and quantitative composition in terms of active substances and both are presented as tablet formulations.
No bioequivalence study has been performed and none is required as a BCS-based biowaiver is applicable to this medicinal product in accordance with Appendix III of CPMP/EWP/QWP/1401/98 Rev. 1/ Corr. Paralief Extra film coated tablets and Panadol Extra film-coated tablets can be considered pharmaceutically equivalent.
The content of the SmPC approved during this decentralised procedure is in accordance with that accepted for the reference product Panadol Extra with the addition of some updates.

IV.2 Pharmacokinetics

The pharmacokinetics of both paracetamol and caffeine are well described and adequately summarised in the clinical dossier.
Paracetamol is rapidly and almost completely absorbed from the gastro-intestinal tract.
Paracetamol is relatively uniformly distributed throughout most body fluids and exhibits variable protein binding. Excretion is almost exclusively renal, in the form of conjugated metabolites.
Caffeine is absorbed readily after oral administration. Maximal plasma concentrations are achieved within one hour and the plasma half-life is about 3.5 hours. 65 - 80% of administered caffeine is excreted in the urine as 1-methyluric acid and 1-methylxanthine.

IV.3 Pharmacodynamics

The pharmacodynamics of paracetamol and caffeine are adequately summarised in the clinical dossier.
Paracetamol is an analgesic and antipyretic agent.
Caffeine is a methylated xanthine and potent stimulant of the central nervous system. Caffeine is a common adjuvant for analgesic drugs such as paracetamol

IV.4 Clinical Efficacy

The efficacy of paracetamol and caffeine for the indications proposed are well established and have been adequately described by the applicant.
SmPC changes:
The indication:

"*Paralief Extra are used for the symptomatic treatment of mild to moderate pain and /or fever.*
This medicine is indicated in adults, the elderly and children aged 12 years and over."
The indication remains almost fully in line with the indication of the reference medicinal product but has been slightly reworded for clarity.
The posology:
"*Adults and adolescents aged 16 years and over:*
1 to 2 tablets up to four times daily. The dose should not be repeated more frequently than every 4 hours.
Do not exceed 8 tablets in 24 hours.
Adolescents aged 12 – 15 years:
One tablet up to four times daily. The dose should not be repeated more frequently than every 4 hours. The daily dose of paracetamol should not exceed 2g/day.

Children
Not recommended for children under 12 years of age.
The posology remains almost fully in line with the posology of the reference product. The dose for children and adolescents aged 12 to 15 years is one tablet up to four times daily which is in line with Ireland's recommendations for paracetamol formulations for this age group.
For specific situations where the maximum daily dose of paracetamol should not exceed 2g (please see the SmPC for details).

IV.5 Clinical Safety
The safety data provided by the applicant is based on literature review. The safety profile of paracetamol and caffeine are well known in combination together. The applicant has given an adequate overview of the safety of paracetamol and caffeine. The Summary of
Product Characteristics (SmPC) and Patient Leaflet (PL) contain the relevant contraindications, safety warnings and have been updated in line with the reference medicinal product and current data relating to the active substances.
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/Caffeine. (RMP: DLP July 2016; Date of final sign off 23/8/2016; Version 1) which is acceptable.
Routine risk minimisation measures are acceptable.
The PSUR is on a 13 year cycle : Next DLP 24/6/2025 and PSUR due 24/9/2025.
Common renewal date
Common renewal date will be 5 years after the finalisation of the procedure.

IV.6 Discussion on the clinical aspects

The legal basis for this application for a Marketing Authorisation for Paralief Extra film coated tablets is a generic application according to Article 10(1) of the Directive 2001/83 EC as amended. The reference medicinal product is Panadol Extra film-coated tablets (PA0678/027/001) authorised in Ireland since 14/06/1994. The two products have the same qualitative and quantitative composition in terms of active substances and both are presented as tablet formulations.

No bioequivalence study has been performed and none is required as a BCS-based biowaiver is applicable to this medicinal product in accordance with Appendix III of the European Medicines Agency Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr). Paralief Extra film coated tablets and Panadol Extra film-coated tablets can be considered to be pharmaceutically equivalent.

The proposed product information (SmPC and PL) has been updated in accordance with the reference product information and with current information pertinent to the active substances.

V. OVERALL CONCLUSIONS

Paralief Extra film coated tablets is a generic form of Panadol Extra film-coated tablets (PA0678/027/001). Panadol Extra is a well-known medicinal product authorised in Ireland since 14/06/1994. Both active substances have been authorised for long periods of time and the safety and efficacy profiles are well-characterised.

The SmPC is consistent with that of the reference product and has been updated with current information pertinent to the active substances.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted considered that Paralief Extra film coated tablets pharmaceutically equivalent to the reference product and has as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

August 2021

VII. UPDATES

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
MAH transfer	CRN009WXZ	SmPC section 7, 8, 10 Package Leaflet New MA Holder: Clonmel Healthcare Ltd. New PA number: PA0126/337/001	N/A	13/08/2021