IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Paracetamol 500 mg Capsules, hard
Paracetamol
PA22871/016/001

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

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Paracetamol 500 mg Capsules, hard, from Azure Pharmaceuticals Ltd on 3rd of June 2022 for the following indication:

For use in the short-term management of mild pain and fever and for symptoms of common colds and flu in adults, the elderly and children aged over 10 years. Paracetamol may also be used in the symptomatic relief of mild to moderate pain associated with osteoarthritis in adults and the elderly, as diagnosed by a doctor.

This application for a marketing authorisation was submitted as a new national procedure application in accordance with Article 10a of Directive 2001/83/EC and is referred to as a well-established use application.

This is medicinal product is not subject to prescription however pack size restrictions apply.

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	Paracetamol 500 mg Capsules, hard
Name(s) of the active substance(s) (INN)	Paracetamol
Pharmacotherapeutic classification (ATC code)	N02BE01
Pharmaceutical form and strength(s)	500 mg Capsules, hard
Marketing Authorisation Number(s) in Ireland (PA)	PA22871/016/001
Marketing Authorisation Holder	Azure Pharmaceuticals Ltd
MRP/DCP No.	IE/H/1143/001/DC
Reference Member State	IE
Concerned Member State	MT

II. QUALITY ASPECTS

II.1. Introduction

This application is for Paracetamol 500 mg Capsules, hard

II.2 Drug substance

The active substance is Paracetamol 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

Each capsules contains 500 mg paracetamol

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 the dosage form, 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 Ph. Eur./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 Paracetamol 500 mg Capsules, hard.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of paracetamol, are well known. As paracetamol is a widely used, well-known active substances, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate. A brief summary of the literature submitted is provided below.

Reference is made to the published scientific literature in the Non-Clinical Overview but the GLP status of these studies cannot be assumed or verified

III.2 Pharmacology

Paracetamol has analgesic and antipyretic effects but only weak anti-inflammatory effect. There is sufficient clinical experience with this active substances and the submission of further non-clinical pharmacology data is not required.

III.3 Pharmacokinetics

The non-clinical pharmacokinetics of paracetamol has been briefly reported from the published literature and discussed in the non-clinical overview. Given the extent of clinical data available for this active substance, no further non-clinical pharmacokinetic data are required.

III.4 Toxicology

The toxicological properties of paracetamol are well known. No non-clinical studies were conducted by the applicant in support of this application. Paracetamol-induced hepatotoxicity is the main toxic effect observed in non-clinical species, hepatotoxicity is a known risk associated with paracetamol overdose clinically. Bibliographic data are inconclusive with respect to genotoxicity and carcinogenicity of paracetamol, but the normal therapeutic use of paracetamol is not associated with genotoxic or carcinogenic risks. Conventional studies using the currently accepted standards for the evaluation of toxicity to reproduction and development are not available. Considering the extensive clinical experience with this active substance, including extensive use in pregnancy, no further non-clinical toxicology data were requested.

III.5 Ecotoxicity/environmental risk assessment

The absence of ERA studies is acceptable on the basis that the approval of this product is not anticipated to increase the environmental exposure to the active substance.

III.6 Discussion on the non-clinical aspects

As paracetamol is a well-known active substance, the non-clinical dossier was bibliographic with no new non-clinical studies conducted by the applicant. No new information was provided that would alter the risk-benefit balance for paracetamol.

IV. CLINICAL ASPECTS

IV.1 Introduction

This application is based on well-established use and therefore the clinical dossier is based upon published literature.

Paracetamol is a well-known active substance with an established efficacy and safety profile.

IV.2 Pharmacokinetics

Paracetamol is rapidly and almost completely absorbed from the gastro-intestinal tract.

Concentration in plasma reaches a peak in 30 - 60 minutes. Plasma protein binding is variable. Plasma half-life is 1 - 4 hours.

Paracetamol is relatively uniformly distributed throughout most body fluids.

Excretion is almost exclusively renal, in the form of conjugated metabolites.

IV.3 Pharmacodynamics

Paracetamol has analgesic and antipyretic actions.

IV.4 Clinical Efficacy

The applicant has provided several appropriate literature references demonstrating that the efficacy of paracetamol is well established in the proposed indications.

IV.5 Clinical Safety

The applicant has provided several appropriate literature references demonstrating that the safety of paracetamol is well established. Undesirable effects listed in the SmPC are:

Body System	Undesirable Effect	Frequency

Paracetamol		
Blood and lymphatic system disorders	Thrombocytopaenia	Very rare
Immune System disorders	Anaphylaxis, Cutaneous hypersensitivity reactions, including, among others, skin rashes, angiodema, Stevens Johnson syndrome and Toxic Epidermal Necrolysis. Very rare cases of serious skin reactions	Very rare
Respiratory, thoracic and mediastinal disorders	Bronchospasm in patients sensitive to aspirin and other NSAIDs	Very rare
Hepatobiliary disorders	Hepatic dysfunction	Very rare

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

Risk Management Plan

Periodic Safety Update Report (PSUR)
With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

IV.6 Discussion on the clinical aspects

The clinical aspects of this medicinal product are well established and acceptable.

V. OVERALL CONCLUSIONS

Paracetamol 500 mg Capsules, hard has a proven chemical-pharmaceutical quality and a well-established and favourable efficacy and safety profile. The applicant has appropriately demonstrated this profile using appropriate bibliographic references.

From a quality perspective the overall assessment outcome of Paracetamol 500 mg Capsules, hard is positive.

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 Paracetamol 500 mg Capsules, hard has demonstrated adequate evidence of efficacy for the approved indication as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

21.03.2027