IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Paracetamol/Ibuprofen 500 mg/200 mg film-coated tablets
Ibuprofen
Paracetamol
PA1113/032/001

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

Name of the product	Paracetamol/Ibuprofen 500 mg/200 mg film-coated tablets
Name(s) of the active substance(s) (INN)	Ibuprofen Paracetamol
Pharmacotherapeutic classification (ATC Code)	N02BE51
Pharmaceutical form and strength(s)	500 mg/200 mg film-coated tablets
Marketing Authorisation Number(s) in Ireland (PA)	PA1113/032/001
Marketing Authorisation Holder	Phoenix Labs Suite 12, Bunkilla Plaza Bracetown Business Park Clonee Co. Meath. Ireland
MRP/DCP No.	IE/H/1428/001
Reference Member State	IE
Concerned Member State(s)	None

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Paracetamol/ibuprofen 500 mg/200 mg film-coated tablets from Clinres Nova d.o.o.

The product is indicated forthe short-term symptomatic treatment of mild to moderate pain, especially for pain that cannot be relieved by the use of ibuprofen or paracetamol alone.

A comprehensive description of the indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC. The reference product is Nurofen Ultima 200 mg + 500 mg film-coated tablets authorized to Reckitt Benckiser (Poland) S.A, in Poland since 1.12.2010.

II. QUALITY ASPECTS

I.1 Introduction

Paracetamol/ibuprofen tablets are white to off white, oblong, biconvex film-coated tablets with dimensions of 21 mm x 10.5 mm (± 0.5 mm) and marked with double circle mark on one side.

The film-coated tablets are packed in PVDC/PVC//Alu blisters or PVDC/PVC//Alu/PET child-resistant blisters.

The other ingredients are:
Tablet core: maize starch, povidone K 30 (E1201), croscarmellose sodium (E468), cellulose microcrystalline (E460), silica colloidal anhydrous (E551), glycerol dibehenate (E471).
Film-coating: opadry white (polyvinyl alcohol-partially hydrolysed, talc, titanium dioxide (E171), glyceryl monocaprylocaprate, sodium laurilsulfate).

The RMS has been assured that acceptable standards of GMP are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product.

I.2 Drug Substance

The proposed drug product contains two active substances: paracetamol and ibuprofen. Both active substances are described in the Ph. Eur. and the CEP procedure is used for both the drug substances. For each of the active substances copies of two CEPs are presented in the documentation.

Paracetamol

According to the Ph. Eur., paracetamol is a white or almost white, crystalline powder. It is sparingly soluble in water, freely soluble in alcohol and very slightly soluble in methylene chloride.

Manufacturing process

CEPs have been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. with additional requirements as stated on the CEPs. The satisfactory quality is generally ensured through the CEP. However, in addition to these tests, the test for microbiological contamination is also included in the DPM specification for paracetamol. Batch analytical data demonstrating compliance with this specification have been provided.

Stability of drug substance

Re-test periods are presented on CEPs.

Ibuprofen

According to the Ph. Eur., ibuprofen is white or almost white, crystalline powder or colourless crystal. It is practically insoluble in water, freely soluble in acetone, in methanol and in methylene chloride. It dissolves in dilute solutions of alkali hydroxides and carbonates.

Manufacturing process

CEPs have been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. with additional requirements as stated on the CEPs. The satisfactory quality is generally ensured through the CEP. However, in addition to these tests, the tests for microbiological contamination and particle size are also included in the DPM specification for ibuprofen. Batch analytical data demonstrating compliance with this specification have been provided.

Stability of drug substance

Re-test periods are presented on CEPs.

I.3 Medicinal Product

The drug product is an immediate release dosage form formulated as a film-coated tablet in one fixed dose combination strength.

The manufacturing process selected, consisting of wet granulation, blending, tablet compression and film coating, is regarded as a standard process. In general, the manufacturing process has been described in adequate detail.

Holding time supported by stability data for bulk film-coated tablets is proposed. It is confirmed that the shelf life of the finished product is calculated according to the Note for guidance on start of shelf-life of the finished dosage form.

The finished product specifications cover appropriate parameters for this dosage form, including acceptable dissolution specification.

Analytical methods are provided together with satisfactory validation data. Provided batch results demonstrate compliance with the proposed finished product specification and batch to batch consistency is confirmed.

The risk assessment report of elemental impurities is enclosed and according to obtained data it can be concluded that there is no risk of any elemental impurities presence in the drug product. The risk evaluation concerning the presence of nitrosamine impurities is considered acceptable. For the bulk tablets stability up to 6 months at storage conditions below 25°C is considered justified and acceptable.

Two types of packaging intended for marketing are proposed (PVC/PVDC//Alu blisters and PVC/PVDC//Alu/PET child-resistant blisters). Information regarding primary and bulk packaging is satisfactory.

Based on the presented stability data the proposed shelf life of 36 months without special storage conditions for Paracetamol/ibuprofen Clinres Nova 500 mg/200 mg film-coated tablets in the proposed packaging is considered acceptable.

I.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Paracetamol/ibuprofen has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substances and the finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

I.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of ibuprofen and of paracetamol as well as those of their combination are well known. As ibuprofen and paracetamol are 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.

I.2 Ecotoxicity/environmental risk assessment (ERA)

The Applicant first provided consumption data of the active substance paracetamol for period of 3 years. From submitted documentation increased consumption is evident and increase in environmental exposure can be expected.

The Applicant updated the response with Phase I and Phase II Environmental Risk Assessments (ERA) for paracetamol, based on published data. All relevant literature has been submitted in the dossier. The assessment concludes that paracetamol is unlikely to pose a significant risk to the environment, which is deemed acceptable.
Considering that both substances are well known with known impact on the environment, the Applicant will not be asked to perform the studies.

IV. CLINICAL ASPECTS

I.1 Introduction

For this generic application, the MAH has submitted two bioequivalence studies, which are discussed below.

I.2 Pharmacokinetics

Bioequivalence studies

Study AKD-P4-861: Randomized, single dose, 2-way crossover bioequivalence study of ibuprofen + paracetamol 200 mg + 500 mg film-coated tables in healthy male volunteers under fasting conditions.

Study AKD-P4-907: Randomized, single dose, 2-way crossover bioequivalence study of ibuprofen/paracetamol 200 mg/500 mg film-coated tablets in healthy male volunteers / fed state.

AUC_{0-t} and C_{max} were defined as primary variables. According to Ibuprofen oral use immediate release formulations 200– 800 mg product-specific bioequivalence guidance
EMA/CHMP/356876/2017 Rev.1* and Paracetamol oral use immediate release formulations product-specific bioequivalence guidance EMA/CHMP/356877/2017 Rev.1*, AUC_{0-t}, C_{max} and T_{max} should be main pharmacokinetic variables for the bioequivalence assessment.
The Applicant provided justification that the bioequivalence studies AKD-P4-861 and AKD-P4-907 were designed before current relevant product-specific bioequivalence guidelines came into effect, and thus the T_{max} was not considered as a main PK parameter. Anyhow, considering both ibuprofen and paracetamol had a difference in median T_{max} being less than 20%, in study AKD-P4-861, which is considered a pivotal study, the primary PK endpoint T_{max} for ibuprofen and paracetamol is considered to be comparable between the Test and Reference Products.

Conclusion on bioequivalence studies:
Based on the submitted bioequivalence studies Paracetamol/ibuprofen 500 mg/200 mg film-coated tablets is considered bioequivalent with Nurofen Ultima 200 mg + 500 mg film-coated tablets.

I.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/ibuprofen.

- Summary table of safety concerns as approved in RMP

Part II: Module SVIII - Summary of the safety concerns

Table 1. Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

Routine pharmacovigilance was suggested and no additional pharmacovigilance activities were proposed by the Applicant, which was endorsed.

Routine risk minimisation measures were considered satisfactory to minimise the risks of this medicinal product.

I.4 Discussion on the clinical aspects

The application contained an adequate review of published clinical data and the bioequivalence has been shown.

II. User consultation

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

V. OVERALL CONCLUSIONS

Based on the review of the data on quality, safety and efficacy, the risk-benefit ratio for the application for Paracetamol/ibuprofen 500 mg/200 mg film-coated tablets was considered positive.

The SmPC, PL and labelling are satisfactory.

Agreement between Member States was reached during the procedure. There was no discussion in the CMDh. The decentralised procedure was finalised with a positive outcome on 23.3.2025.

No conditions pursuant to Article 21a or 22 of Directive 2001/83/EC have been made during the procedure.

VI. REVISION DATE

07/07/2025

VII. UPDATES

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
RMS transfer	From HR/H/0282/001/DC to IE/H/1428/001	N/A	07/07/2025	07/07/2025