IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Brupro for Children Six Plus 200 mg/5 ml oral suspension
Ibuprofen
PA0074/067/005

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 Brupro for Children 100 mg/5 ml oral suspension and Brupro for Children Six Plus 200 mg/5 ml oral suspension, from Rowa Pharmaceuticals Limited on 11th March 2022 for:

Brupro for Children 100 mg/5 ml oral suspension
Reduction of fever and relief of mild to moderate pain, such as cold and flu symptoms, teething pain, headache, sprains and strains and to ease the pain of sore throats and earache

- in children weighing at least 5 kg from 3 months of age to 12 years of age.

Brupro for Children Six Plus 200 mg/5 ml oral suspension

For the short-term symptomatic treatment of mild to moderate pain

For the short-term symptomatic treatment of fever

- in children weighing at least 20kg from 6 years to 12 years of age.

This application for a national marketing authorisation was submitted in accordance

with Article 10a of Directive 2001/83/EC, referred to as a 'well-established use' application. The Marketing Authorisation Holder is not required to provide the results of pre-clinical and clinical trials as the product is a well-known medicinal product and this is supported by bibliographic literature

Both products are not subject to a medical prescription and are supplied through pharmacies only.

The Summary of Product Characteristics (SmPC) for these medicinal products is available on the HPRA's website at www.hpra.ie.

Name of the products	Brupro for Children 100 mg/5 ml oral suspension Brupro for Children Six Plus 200 mg/5 ml oral suspension
Name(s) of the active substance(s) (INN)	Ibuprofen
Pharmacotherapeutic classification (ATC code)	M01AE01
Pharmaceutical form and strength(s)	Oral suspension; 100 mg/5 ml, 200 mg/5 ml
Marketing Authorisation Number(s) in Ireland (PA)	PA0074/067/004; PA0074/067/005
Marketing Authorisation Holder	Rowa Pharmaceuticals Limited

II. QUALITY ASPECTS

II.1. Introduction

This application is for Brupro for Children 100 mg/5 ml oral suspension and Brupro for Children Six Plus 200 mg/5 ml oral suspension.

II.2 Drug substance

The active substance is Ibuprofen, 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

Composition of the medicinal product

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 guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)

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 liquid preparations for oral use, 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.7 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.8 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 and Pharmaceutical 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 Brupro for Children 100 mg/5 ml oral suspension and Brupro for Children Six Plus 200 mg/5 ml oral suspension.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Ibuprofen is a well-known non-steroidal anti-inflammatory drug (NSAID), that has been in widespread therapeutic use for many years. The sponsor has provided a non-clinical overview based on relevant scientific literature. This is acceptable in accordance with Article 10a of Directive 2001/83/EC as amended. The GLP status of these bibliographic studies is unknown.

III.2 Pharmacology

Ibuprofen is a propionic acid derivate, an NSAID with analgesic, antipyretic and anti-inflammatory properties. Ibuprofen is a potent inhibitor of prostaglandin synthesis, via non-selective inhibition of cyclooxygenase. In addition to the inhibition of cyclooxygenase, ibuprofen influences the expression/activity of different transcription factors and cellular kinases that may account for cyclooxygenase independent therapeutic actions of Ibuprofen. The anti-inflammatory, analgesic and antipyretic actions of ibuprofen have been shown in many experimental animal studies.

As the pharmacological properties of ibuprofen are well-known, no additional animal pharmacology studies have been performed in support of this application. A detailed literature review has been provided and this is considered acceptable from a non-clinical perspective for this well-established use application.

III.3 Pharmacokinetics

As the pharmacokinetic properties of ibuprofen are well-known, no further animal pharmacokinetic studies have been performed in support of this application. A detailed literature review has been provided and this is acceptable from a non-clinical perspective for this well-established use application.

III.4 Toxicology

The gastrointestinal tract is a major target organ of toxicity for all NSAIDs. Prostaglandins increase protective mucous production, decrease acid secretion and increase mucosal blood flow in the gastric mucosa, effects which are reversed when prostaglandin synthesis is inhibited, facilitating peptic ulcer formation.

As the toxicological properties of ibuprofen are well-known, no further animal toxicology studies have been performed in support of this application. A detailed literature review has been provided and no new safety concerns have been identified for. This acceptable from a non-clinical perspective for this well-established use application.

III.5 Ecotoxicity/environmental risk assessment

The log K_{OW} for ibuprofen is below the trigger value of 4.5, therefore additional screening for persistence, bioaccumulation and toxicity is not required.

The $PEC_{surfacewater}$ for ibuprofen is greater than the action limit of 0.01µg/L, and a Phase II environmental fate and effect analysis was conducted based on publically available data in the scientific literature. A risk of toxicity to aquatic organisms was identified and recommendations regarding proper disposal are included in the product information.

III.6 Discussion on the non-clinical aspects

As the pharmacological, pharmacokinetic and toxicological properties of the active substance are well-known, the approval of Brupro for children 100mg/5ml and 200mg/5ml is supported from a non-clinical perspective.

IV. CLINICAL ASPECTS

IV.1 Introduction

Ibuprofen, a non-steroidal anti-inflammatory drug (NSAID), is a well-known active substance with established efficacy, safety and tolerability. Ibuprofen has been in widespread therapeutic use for many years. The applicant has provided a clinical

overview based on relevant scientific literature. This is acceptable in accordance with Article 10a of Directive 2001/83/EC as amended.

The content of the SmPC approved during the national procedure is in accordance with that accepted for similar ibuprofen products on the market.

No new clinical studies were completed by the applicant, which is acceptable for this type of application, in accordance with Article 10a of Directive 2001/83/EC as amended.

IV.2 Pharmacokinetics

On oral application, ibuprofen is partly absorbed in the stomach and afterwards completely in the small intestine. Peak plasma levels following oral administration of an immediate release pharmaceutical form are reached after 1-2 hours. Following hepatic metabolisation (hydroxylation, carboxylation, conjugation), the pharmacologically inactive metabolites are completely eliminated, mainly renally (90 %), but also with the bile. The elimination half-life in healthy individuals and those with liver and kidney diseases is 1.8 - 3.5 hours. Plasma protein binding is about 99 %.
Data from the literature indicate that the absorption, metabolism and elimination of ibuprofen in children proceeds in the same way as in adults

Renal impairment
Ibuprofen and its metabolites are primarily eliminated by the kidneys (~90%). Ibuprofen is a racemic mixture of [+] S- and [-] R-enantiomers. For patients with renal impairment decreased protein binding, increased plasma levels for total ibuprofen and unbound S-ibuprofen, higher AUC values for S-ibuprofen and increased enantiomeric AUC (S/R) ratios as compared with healthy controls have been reported. In end-stage renal disease patients receiving dialysis the mean free fraction of ibuprofen was about 3% compared with about 1% in healthy volunteers. Severe impairment of renal function may result in accumulation of ibuprofen metabolites. The significance of this effect is unknown. The metabolites can be removed by haemodialysis.

Hepatic impairment
Alcoholic liver disease with mild to moderate hepatic impairment did not result in substantially altered pharmacokinetic parameters. Hepatic disease can alter the disposition kinetics of ibuprofen. In cirrhotic patients with moderate hepatic impairment (Child Pugh's score 6-10) an average 2-fold prolongation of the half-life was observed and the enantiomeric AUC ratio (S/R) was significantly lower compared to healthy controls suggesting an impairment of metabolic inversion of R-ibuprofen to the active S-enantiomer.

IV.3 Pharmacodynamics

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) that has demonstrated its efficacy in the common animal experimental inflammation models by inhibition of prostaglandin synthesis. In humans, ibuprofen reduces inflammatory pain, swellings and fever. In addition, ibuprofen reversibly inhibits platelet aggregation.

Experimental data suggest that ibuprofen may competitively inhibit the effect of low dose acetylsalicylic acid (aspirin) on platelet aggregation when they are dosed concomitantly. Some pharmacodynamic studies show that when single doses of ibuprofen 400 mg were taken within 8 h before or within 30 min after immediate release acetylsalicylic acid dosing (81 mg), a decreased effect of acetylsalicylic acid on the formation of thromboxane or platelet aggregation occurred. Although there are uncertainties regarding extrapolation of these data to the clinical situation, the possibility that regular, long-term use of ibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid cannot be excluded. No clinically relevant effect is considered to be likely for occasional ibuprofen use.

IV.4 Clinical Efficacy

The clinical efficacy of ibuprofen is well established and has been demonstrated in the symptomatic treatment of mild to moderate pain such as pain through toothache, headache, and in the symptomatic treatment of fever.

The analgesic dose for children is 7 to 10 mg/kg per dose with a maximum of 30 mg/kg/day. Brupro for Children 100 mg/5 ml and Brupro for Children Six Plus 200 mg/5 ml contain ibuprofen which showed in an open-label study an onset of antipyretic action after 15 minutes and decreased fever in children for up to 8 hours.

IV.5 Clinical Safety

The safety profile of ibuprofen from the literature has been described in the clinical overview submitted by the applicant and is reflected in the SmPC.

Risk Management Plan (usual pharmacovigilance requirements +/- additional requirements)

A Risk Management Plan, version 0.1, dated 2nd February 2021 has been submitted, 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 Brupro for Children 100mg/5ml Oral Suspension and Brupro for Children Six Plus 200mg/5ml Oral Suspension. Based on consideration of the identified risks, the potential risks and the need for additional information on the medicinal product, it is concluded that routine pharmacovigilance and risk minimisation measures are sufficient.

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.

IV.6 Discussion on the clinical aspects

The applicant has submitted sufficient clinical information to support authorisation of these medicinal products. From a clinical perspective the benefit/risk profile of the products is considered favourable.

V. OVERALL CONCLUSIONS

Brupro for Children 100 mg/5 ml Oral Suspension and Brupro for Children Six Plus 200 mg/5 ml oral supsension contain ibuprofen, a well-known medicinal product with an established efficacy and safety profile.

The summary of product characteristics (SmPC) is consistent with those of similar products available on the market.

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 Brupro for Children 100 mg/5 ml oral suspension and Brupro for Children Six Plus 200 mg/5 ml oral suspension demonstrated adequate evidence of efficacy for the approved indication(s) as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

5 years from date of authorisation.

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