IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Fenopine for Children Six Plus Strawberry 200mg/5ml Oral Suspension
Ibuprofen
PA0281/088/006

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 for Fenopine for Children Six Plus Strawberry 200mg/5ml Oral Suspension, from Pinewood Laboratories Ltd on 18th December 2020 indicated for:

Children under 12 years

- rheumatic or muscular pain, headache, dental pain, feverishness (including post-immunisation pyrexia), symptoms of cold and influenza.

Over 12 years

-rheumatic or muscular pain, pain of non-serious arthritic conditions, backache, neuralgia, migraine, headache, dental pain, dysmenorrhoea, feverishness, symptoms of colds and influenza.

This national application for a marketing authorisation for Fenopine for Children Six Plus Strawberry 200mg/5ml Oral Suspension is a duplicate application of Fenopine 200 mg/5 ml Oral Suspension (PA 0281/088/005) which was submitted to HPRA in accordance with Article 10(3) of Directive 2001/83/EC and is referred to as a 'hybrid' application. The European reference product is Nurofen 200mg coated tablets (PL00327/0146) authorised in the UK since 15th July 2003. Bioequivalence has been shown to the reference product authorised in Ireland – Nurofen 200mg coated tablets (PA0979/032/006) with regard to CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **.

The product is subject to prescription which may be renewed (B). It is for supply through pharmacies and for promotion to healthcare professionals only.

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	Fenopine for Children Six Plus Strawberry
Name(s) of the active substance(s) (INN)	Ibuprofen
Pharmacotherapeutic classification (ATC code)	M01AE01 ibuprofen
Pharmaceutical form and strength(s)	Oral suspension 200 mg/5ml
Marketing Authorisation Number(s) in Ireland (PA)	PA0281/088/006
Marketing Authorisation Holder	Pinewood Laboratories Ltd

II. QUALITY ASPECTS

II.1. Introduction

This application is for Fenopine for Children Six Plus Strawberry 200mg/5ml 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 (Each 5ml contains 200mg Ibuprofen).

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 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.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 Fenopine for Children Six Plus Strawberry 200mg/5ml Oral Suspension.

III. NON-CLINICAL ASPECTS

III.1 III.1 Introduction

This active substance is the same as that present in Nurofen 200mg coated tablets (PL00327/0146) on the European market. 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.

III.5 Ecotoxicity/environmental risk assessment

An Environmental Risk Assessment has not been performed as this product is intended for generic substitution and therefore will not result in an increase of risk to the environment during use, storage and disposal.

III.6 Discussion on the non-clinical aspects

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. Pharmacodynamic, pharmacokinetic and toxicological properties of ibuprofen are well known and preclinical data have been superceded by clinical experience.

IV. CLINICAL ASPECTS

IV.1 Introduction

Ibuprofen is a well-known active substance with established efficacy and tolerability.

This national application for a marketing authorisation for Fenopine for Children Six Plus Strawberry 200mg/5ml Oral Suspension is a duplicate application of Fenopine 200 mg/5 ml Oral Suspension (PA0281/088/005) which was submitted to HPRA in accordance with Article 10(3) of Directive 2001/83/EC (a 'hybrid' application) and authorised following the Mutual Recognition procedure UK/H/3267/002/E/001.

The European reference product is Nurofen 200mg coated tablets (PL00327/0146) authorised in the UK since 15th July 2003. A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out. Ibuprofen 200mg/5ml Oral Suspension (Pinewood Laboratories Ltd, Ireland), was compared to the reference product Nurofen 200mg Tablets authorised in Ireland (PA0979/032/006, Reckitt Benckiser, Ireland). Based on the pharmacokinetic parameters of active substance ibuprofen, the reference tablet Nurofen 200mg Tablets (Reckitt Benckiser, Ireland) and test tablet Ibuprofen 200mg/5ml Oral Suspension (Pinewood Laboratories Ltd, Ireland) are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **).

The HPRA has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

The content of the SmPC approved during the national procedure is in accordance with that accepted for the reference product Nurofen 200mg Tablets (Reckitt Benckiser, UK and Ireland).

IV.2 Pharmacokinetics

Absorption
On oral application ibuprofen is partly absorbed in the stomach and then completely in the small intestine, peak serum concentrations occurring 1 2 hours after oral administration of a normal-release pharmaceutical form.

Distribution
Ibuprofen is rapidly distributed throughout the whole body. The plasma protein binding is approximately 99%.

Metabolism
Ibuprofen is metabolised in the liver (hydroxylation, carboxylation).

Elimination
Ibuprofen is metabolised in the liver into two major metabolites with primary excretion via the kidneys. Excretion by the kidney is both rapid and complete. Elimination half-life is approximately 2 hours.

IV.3 Pharmacodynamics

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

IV.4 Clinical Efficacy

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

IV.5 Clinical Safety

No new safety data have been submitted or required for this type of application. As ibuprofen is a well-known product with an acceptable adverse event profile, this is satisfactory.

Risk Management Plan
The applicant 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 Fenopine for Children Six Plus Strawberry 200mg/5ml Oral Suspension. Routine pharmacovigilance and risk minimisation activities are proposed for all safety concerns. The applicant is requested to ensure it maintains the RMP in line with the latest SmPC updates and maintains regular reviews.

Summary table of safety concerns as approved in RMP

Summary of safety concerns	
Important identified risks	• Serious gastrointestinal toxicity including bleeding, ulceration or perforation • Hypersensitivity reactions including anaphylaxis • Bronchospasm in patients with a history of bronchial asthma or allergic disease • Cardio-renal effects (hypertension, oedema) • Use during third trimester of pregnancy (including risk of premature closure of patent ductus arteriosus, delayed labour, increased bleeding tendency) • Hepatic disorders • Renal disorders • Serious skin reactions • Interactions with anticoagulants, methotrexate, lithium, cardiac glycosides
Important potential risks	• Arterial thrombotic events (e.g. myocardial infarction, stroke) • Impaired female fertility • Increased risk of aseptic meningitis in patients with systemic lupus erythematosus and mixed connective tissue disease
Missing information	• Use during 1st and 2nd trimesters of pregnancy • Use during breast feeding • Exposure in children below 3 months of age

PSURs
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.
- For medicinal products that do not fall within the categories waived of the obligation to submit routine PSURs by the revised pharmacovigilance legislation, the MAH should follow the DLP according to the EURD list.

IV.6 Discussion on the clinical aspects

For this marketing authorisation, reference is made to the clinical studies and experience with the reference product Nurofen 200mg tablets from Reckitt Benckiser. This national application for a marketing authorisation is a duplicate application of Fenopine 200 mg/5 ml Oral Suspension (PA 0281/088/005) which was submitted to HPRA in accordance with Article 10(3) of Directive 2001/83/EC and is referred to as a 'hybrid' application. The European reference product is Nurofen 200mg coated tablets (PL00327/0146) authorised in the UK since 15th July 2003. Bioequivalence has been shown to the reference product authorised in Ireland – Nurofen 200mg coated tablets (PA0979/032/006) with regard to CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **.

Fenopine for Children Six Plus Strawberry 200mg/5ml Oral Suspension is a generic form of Nurofen 200mg tablets from Reckitt Benckiser (PA0979/032/0060 which is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the CHMP guidance documents.

The SmPC and PIL are consistent with that of the reference product.

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

V. OVERALL CONCLUSIONS

The HPRA, on the basis of the data submitted considered that Children Six Plus Strawberry 200mg/5ml Oral Suspension demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

VII. UPDATES

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

SCOPE	PROCEDURE NUMBER	PRODCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
National 1B variation type 1B. The scope of this type 1B National variation is to reclassify/switch Fenopine for Children Six Plus Strawberry 200mg/5ml Oral Suspension from POM to OTC(P) supply	Crn009HHN	SmPC/PL/label The indications and posology in sections 4.1 and 4.2 have been revised to reflect the OTC(P) supply status.	19/06/2020	