IPAR

Health Products Regulatory Authority
PUBLIC ASSESSMENT REPORT FOR A MEDICINAL PRODUCT FOR HUMAN USE

Scientific discussion

Easofen for Children Strawberry 100mg/5ml Oral Suspension
&
Easofen for Children Six Plus Strawberry 200mg/5ml Oral Suspension
IBUPROFEN
PA126/60/3-4

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.

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for:

Easofen for Children Strawberry 100mg/5ml Oral Suspension indicated for the 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 aged between 3 months and 12 years of age and Easofen for Children Six Plus Strawberry 200mg/5ml Oral Suspension indicated for the short-term symptomatic treatment of mild to moderate pain and for the short-term symptomatic treatment of fever in children aged 6 to 12 years from Acorn Regulatory Consultancy Services Limited on 11th July 2014

This application for a national marketing authorisation was submitted in accordance with Article 10(1) of Directive 2001/83/EC and is referred to as a “generic” application.

Easofen for Children Strawberry 100mg/5ml Oral Suspension and Easofen for Children Six Plus Strawberry 200mg/5ml Oral Suspension have been shown to be bioequivalent to Junifen oral suspension 2% of Reckitt Benckiser Healthcare Limited S.A.

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

Name of the product	Easofen for Children Strawberry 100mg/5ml Oral Suspension and Easofen for Children Six Plus Strawberry 200mg/5ml Oral Suspension

Name(s) of the active substance(s) (INN)	IBUPROFEN
Pharmacotherapeutic classification (ATC code)	M01AE01
Pharmaceutical form and strength(s)	100mg/5ml & 200mg/5ml Oral Suspension
Marketing Authorisation Number(s) in Ireland (PA)	PA 126/60/3-4
Marketing Authorisation Holder	Clonmel Healthcare Ltd

II QUALITY ASPECTS

II.1. Introduction

This application is for Easofen for Children Strawberry 100mg/5ml Oral Suspension snd Easofen 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

The drug products are oral suspensions.

Easofen for Children Strawberry 100mg/5ml Oral Suspension contains 100mg Ibuprofen per 5ml.

Easofen for Children Six Plus Strawberry 200mg/5ml Oral Suspension contains 200mg Ibuprofen per 5ml.

The other ingredients are: Liquid Maltitol, Citric Acid anhydrous, Sodium Citrate
Sodium benzoate (E211), Sodium Chloride, Sodium Saccharin, Hypromellose,
Xanthan gum, Strawberry Flavour (natural flavouring preparations, maize maltodextrin, triethyl citrate (E1505), propylene glycol (E1520) and benzyl alcohol), Glycerol (E422), Purified Water

The 200mg /5ml product also contains Thaumatin (E957)

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/*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 have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The product is presented as an amber coloured polyethylene terephthalate (PET) bottle with a child-resistant closure, fitted with a low density polyethylene stopper. The product is supplied with a 5ml oral syringe, comprising of a high-density polyethylene piston and a polypropylene barrel. The oral syringe is graduated in 0.25ml steps up to 5ml

Evidence has been provided that the packaging complies with Ph. Eur.requirements and EU legislation for use with foodstuffs .

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 demonstrating the stability of the product for 3 years with no special storage conditions and for 6 months after first opening when stored below 25 °C

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 Easofen for Children Strawberry 100mg/5ml Oral Suspension and Easofen for Children Six Plus Strawberry 200mg/5ml Oral Suspension.

III NON-CLINICAL ASPECTS

This active substance is a generic formulation of Junifen oral suspension 2% manufactured by Reckitt Benckiser Healthcare Limited on the European market since March 2000. 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

These are generic applications submitted under article 10(1) of Directive 2001/83/EC. Bioequivalence to Junifen 2% oral suspension of Reckitt Benckiser is claimed.

The indications of the SmPCs approved during the national procedure are in accordance with those accepted for the Irish reference products Nurofen for Children Strawberry 100mg/5ml Oral Suspension and Nurofen for Children Six Plus 200mg/5ml Oral Suspension respectively, both marketed by Reckitt Benckiser Ireland Ltd.

For this generic application, the applicant has submitted a 3 way crossover bioequivalence study in which the pharmacokinetic profile of the test products Ibuprofen 2% Suspension and Ibuprofen 4% Suspension, both developed by Farmalider, S.A., are compared with the pharmacokinetic profile of the reference product Junifen 2% oral suspension of Reckitt Benckiser Healthcare S.A.

The IMB has been assured that the test products used in the bioequivalence study, Ibuprofen 2% oral suspension and Ibuprofen 4% oral suspension, are identical to the products intended for marketing.

For Easofen for Children Strawberry 100mg/5ml, the European reference product is Junifen Suspension Oral 2% of Reckitt Benckiser authorised in Spain since 2000. The Irish reference product is Nurofen for Children Strawberry 100mg/5ml Oral Suspension also of Reckitt Benckiser Ireland Ltd. Bioequivalence has been shown to the European reference product Junifen Suspension Oral 2%.

For Easofen for Children Six Plus Strawberry 200mg/5ml, the European reference product is Junifen Suspension Oral 2% of Reckitt Benckiser authorised in Spain since 2000. The Irish reference product is Nurofen for Children Six Plus Strawberry 200mg/5ml Oral Suspension also of Reckitt Benckiser Ireland Ltd. Bioequivalence has been shown to the European reference product Junifen Suspension Oral 2%.

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

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

IV.2 Pharmacokinetics

The pharmacokinetics of ibuprofen is well understood and has been reviewed in the clinical summary and the Clinical Expert is appropriately medically qualified.

The current Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98/Rev. 1 states in relation to drugs that are racemates, that chiral bioanalytical method is required when (1) the enantiomers exhibit different pharmacokinetics, (2) the enantiomers exhibit pronounced difference in pharmacokinetics and (3) the exposure of enantiomers is modified by a diference in the rate of absorption. For ibuprofen, all these conditions are fulfilled, therefore this study was performed according to this guideline, using a chiral bioanalytical method and measuring the concentrations of both enantiomers. A randomised, open-label, 3-way crossover bioequivalence clinical trial of three formulations of ibuprofen 400mg was carried out. Ibuprofen 2% Suspension and Ibuprofen 4% Suspension of Laboratories Farnaldier S.A., were compared to the reference product Junifen 100mg/5ml oral suspension of Reckitt Benckiser Healthcare S.A. 24 healthy male and female adult subjects were enrolled into the study. The dose given was 400mg. Samples were taken at baseline, 15min, 30min, 45min, 1h, 1h15min, 1h30min, 2h, 2h30min, 3h, 3h30min, 4h, 6h, 8h, 10h, 12h after the administration of each of the products. An adequate washout period of 7 days was maintained between treatments. Data on all subjects was analysed. The primary parameters were C_{max}, AUC 0-t and extrapolated AUC 0-∞. ANOVA and 90% confidence intervals were calculated for the mean ratios of AUC and C_{max} after log transformation.The 90% confidence intervals for the log-transformed pharmacokinetic variables C_{max} and AUC for R-ibuprofen and S-ibuprofen fall within the conventional bioequivalence range of 80-125%. Based on the pharmacokinetic parameters of the active substance iburofen, the reference product Junifen 2% oral suspension, Ibuprofen 2% oral suspension and Ibuprofen 4% oral suspension are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the current bioequivalence guidelines.
After oral administration ibuprofen is partly absorbed in the stomach and afterwards completely in the small intestine. After hepatic metabolism (hydroxylation, carboxylation, conjugation) the pharmacologically inactive metabolites are eliminated completely, mainly renally (90%), as well as via the biliary route. The elimination half life for healthy persons as well as for patients suffering from hepatic or renal diseases is 1.8 to 3.5 hours.

The European reference product in both applications is Junifen Suspension Oral 2% authorised in Spain since 2000. The reference product used in the bioequivalence study (Study 2012-002310-40) is also Junifen Suspension Oral 2% manufactured by Reckitt Benckiser Healthcare S.A.

No special studies on pharmacokinetics have been carried out in children. Literature data confirm that the absorption, metabolism and elimination of ibuprofen in children proceeds in the same way as in adults.

IV.3 Pharmacodynamics

Ibuprofen is a non-steroidal anti-inlammatory drug (NSAID) that, in the conventional animal-experiment inflammation models, has proven to be effective via prostaglandin-synthesis inhibition. In humans, ibuprofen reduces inflammatory pain, swellins and fever. Furthermore, ibuprofen reversibly inhibits platelet aggregation.

Experimental data suggest that ibuprofen may inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are used concomitantly. In one study, when a single dose of ibuprofen 400mg was taken within 8 h before or within 30 min after immediate release acetlsaliclic acid dosing (81mg), a decreased effect of ASA on the formation of thromboxane or platelet aggregation occurred. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusion can be made for regular ibuprofen use, and 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 no additional clinical studies to demonstrate these have been included in the application. This is appropriate for this type of application.

IV.5 Clinical Safety

The clinical safety of ibuprofen is well established, and no additional clinical studies to demonstrate these have been included in the application. This is appropriate for this type of application.

The marketing authorisation holder (MAH) submitted a summary describing the Pharmacovigilance System, including confirmation of the availability of an EU Qualified Person for Pharmacovigilance (EU-QPPV) and the means for notification of adverse reaction reports in the EU or from a Third Country.

A Risk Management Plan has been provided. All known and identified risks as well as interactions are sufficiently covered in the respective sections of the SmPC. No additional concerns have been identified.

The applicant should follow the PSUR submission cycle as adopted in the final version of the European Union Reference Dates (EURD) list.

IV.6 Discussion on the clinical aspects

As this is a generic application under Article 10(1) of Directive 2001/83/EC, additional non-clinical and clinical studies to demonstrate efficacy and safety are not required. The applicant has conducted an appropriate bioequivalence study to demonstrate equivalence between the test and reference products.

The benefit/risk profile of the product is positive.

V OVERALL CONCLUSIONS

From a quality, non-clinical and clinical perspective, the overall assessment outcome of Easofen for Children Strawberry 100mg/5ml Oral Suspension and Easofen for Children Six Plus Strawberry 200mg/5ml Oral Suspension is positive.

Easofen for Children Strawberry 100mg/5ml Oral Suspension and Easofen for Children Six Plus Strawberry 200mg/5ml Oral Suspension are generic forms of Junifen Suspension Oral 2% of Reckitt Benckiser authorised in Spain since 2000. Junifen Suspension Oral 2% 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 SmPCs are consistent with those of the reference products.

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 Easofen for Children Strawberry 100mg/5ml Oral Suspension and Easofen for Children Six Plus Strawberry 200mg/5ml Oral Suspension were the same as the reference

product and therefore granted a national marketing authorisation.