IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

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 Tefin 75 mg and 150 mg Suppositories, from Carysfort Healthcare Limited on 31st August 2012 for the symptomatic treatment of mild to moderate pain and fever.

This applicationfor a marketing authorisation was submitted nationally in accordance with Article 10a of Directive 2001/83/EC and is referred to as a well established use application. This means that that the Marketing Authorisation Holder is not required to provide the results of pre-clinical and clinical trials as the product is a generic medicinal product and this is supported by bibliographic literature.

The prescription status is not subject to medical prescription.

The Summary of Product Characteristics for (SPC) for this medicinal product is available on the HPRA's website at www.hpra.ie

Name of the product	Tefin 75mg and 150 mg Suppositories
Name(s) of the active substance(s) (INN)	IBUPROFEN
Pharmacotherapeutic classification (ATC code)	M01AE01
Pharmaceutical form and strength(s)	75mg and 150mg Suppositories
Marketing Authorisation Number(s) in Ireland (PA)	PA1684/1/1-2
Marketing Authorisation Holder	Carysfort Healthcare Limited

II. QUALITY ASPECTS

II.1. Introduction

This application is for Tefin 75 mg and 150 mg Suppositories.

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 manufacturers of the active substance hold valid Certificates of Suitability for the active.

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

Brief description of the dosage form

The suppositories are lipophilic suppositories and in addition to the active have only one excipient; hard fat.

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 site.

The manufacturing process has been validated according to relevant European and ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)

The sole excipient, hard fat, complies with its Ph. Eur. monograph and is therefore considered adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for suppositories and rectal dosage forms, 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 suitable 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 in blisters of aluminium/ polyethylene. The blisters are packaged in an outer cardboard box with either 10 or 100 suppositories in each.

Evidence has been provided that aluminium/ polyethylene blisters comply with both Ph. Eur. and 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 demonstrating the stability of the product for 5 years 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 Tefin 75 mg and 150 mg Suppositories.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Considering the well-known state of ibuprofen, the applicant has provided a non-clinical application that is completely based on relevant scientific literature.
The GLP status of the studies was not declared in the majority of publications.

However, nearly all of the studies were conducted in renowned laboratories in developed countries. Consequently, it can be suggested that the general GLP rules should be observed.

III.2 Pharmacology

Ibuprofen is a potent, efficacious and well established non-steroidal anti-inflammatory drug (NSAID) that has been in widespread therapeutic use for many years. It is well tolerated with a safety profile at least equal to that of any other commonly used NSAID.

Ibuprofen appear to be associated principally with the inhibition of prostaglandin synthesis by inhibiting cyclooxygenase in a non-selective way. In addition to the inhibition of cyclooxygenase, ibuprofen influences the expression/activity of different transcription factors, cellular kinases and heat shock proteins that may account for cyclooxygenase independent actions seen with the therapeutic action of Ibuprofen. The analgesic and antipyretic action of ibuprofen has been was shown in many experimental animal studies.

As the pharmacological, pharmacokinetic and toxicological properties of the active substance are well-known, no additional animal pharmacology studies have been performed using the proposed clinical formulation. This is considered to eb acceptable from a non-clinical perspective.

III.3 Pharmacokinetics

Ibuprofen is well absorbed orally from the rectal formulation, with peak plasma levels usually occurring within 1 to 2 hours. It is rapidly metabolized and eliminated in the urine. The excretion of ibuprofen is virtually complete 24 hours after the last dose.

As the pharmacological, pharmacokinetic and toxicological properties of the active substance are well-known, no further animal pharmacokinetic studies have been performed using the proposed clinical formulation. A detailed up-to-date literature review has been provided that outlines all known relevant pharmacokinetic data for Ibuprofen. This is considered to eb acceptable from a non-clinical perspective.

III.4 Toxicology

As the pharmacological, pharmacokinetic and toxicological properties of the active substance are well-known, no further animal toxicology studies have been performed using the proposed clinical formulation. A detailed up-to-date literature has been provided that outlines all known safety concerns for the active substance - Ibuprofen. This is considered to be acceptable from a non-clinical perspective.

III.5 Ecotoxicity/environmental risk assessment

Products containing ibuprofen have long been approved in all countries of the EU and it is supposed that the total consumption of ibuprofen is not increased significantly by introducing these new formulations to the market. No environmental risk assessment is therefore considered necessary.

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 Tefin 75 mg and 150 mg Suppositories is supported from a non-clinical perspective.

IV. CLINICAL ASPECTS

IV.1 Introduction

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

IV.2 Pharmacokinetics

The applicant performed a bioavailability study to determine the relative bioavailability of ibuprofen suppositories (150 mg) in comparison to an ibuprofen oral suspension (150 mg)

Suppositories and the oral suspension are bioequivalent regarding the extent of absorption, although the AUC after rectal administration of ibuprofen was slightly lower than those after oral administration corresponding to available published data on rectal pharmacokinetics of ibuprofen indicating 5-10% lower extent of absorption than after oral administration.

Suppositories showed a lower bioavailability regarding rate of absorption than the reference suspension. This is probably because the absorption is mostly prolonged in comparison to oral administration. The differences are not important for clinical use with repeated administration.

IV.3 Pharmacodynamics

The main mechanism of action of ibuprofen seems to be the inhibition of cyclooxygenase activity. Ibuprofen is a non-specific cyclooxygenase inhibitor.

Besides the enzyme inhibition, cyclooxygenase independent actions were observed. It seems to be possible that also these mechanisms are part of the
therapeutic action of ibuprofen.
The analgesic and antipyretic action of ibuprofen was shown in experimental and clinical studies, compared with placebo and reference treatments.
It should be taken into consideration that the analgesic effect may depend on gender (males > females), and the antipyretic effect in children may depend on age (young children > older children). The antipyretic effect is dose-dependent as shown in several clinical studies.

IV.4 Clinical Efficacy

As this is a well established use application, the applicant has documented effects of ibuprofen through reference to published studies.
Ibuprofen decreases fever significantly better than placebo as shown in several studies.Ibuprofen did not decrease significantly the risk of a further febrile seizure in children with a history of febrile seizures. The recurrence of febrile seizures depends on age, high temperature at fever of onset, and high temperature during the episode of fever.
Ibuprofen is at least as effective as paracetamol as antipyretic agent.
Iburprfoen has been shown to be an effective analgesis and anyipyrtetic.

IV.5 Clinical Safety

As this is a well established use application, the applicant has documented effects of ibuprofen through reference to published studies.
Based on the data of 1,125 children treated with ibuprofen for pain or fever, a frequency ranking of adverse events was compiled. Adverse events with a frequency > 10 % (=very common) were not detected. Common adverse events (1-10%) were adverse gastrointestinal and skin symptoms, uncommon (0.1-1%) were adverse events in the central nervous system and sensory organs, and adverse gastrointestinal symptoms, rarely (0.01-0.1%) reported were adverse gastrointestinal and skin symptoms, respiratory, metabolic and adverse eye symptoms. The adverse events were collected independent on actual causal relationship, but especially in gastrointestinal, dermal and central nervous adverse events a causality to ibuprofen administration must be taken into consideration. Very rare adverse events (< 0.01%) cannot be determined in a patient group smaller than 10,000 patients.

The safety of ibuprofen is well known and the SmPC refelfcts the known safety of the drug.

Risk Management Plan:
As Ibuprofen is well established no Risk Management Plan is proposed. The product will be subject to pharmacovigilance according to usual requirements.

Proposed next Data Lock Point June 2013. For 3 yearly PSUR cycle therafter (unless new PV regulations stipulate that PSURs are no longer required for ibuprofen products).

The Marketing Authorisation Holder submitted a set of documents describing the Pharmacovigilance System, including information on 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.

IV.6 Discussion on the clinical aspects

The safety and efficiacy of ibuprofen are well known

V. OVERALL CONCLUSIONS

Benefit/Risk Assessment and Recommendation
From a quality perspective the overall assessment outcome for Tefin 75 mg and 150 mg Suppositories is positive.

Using the published literature, the applicant has documented the safety and efficacy of ibuprofen in the form of Tefin suppositories.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations. Tefin 75 mg and 150 mg Suppositories 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

December 2020

VII. UPDATES

Procedure number	Product Information affected	Date of start of procedure	Date of end of procedure	Approval/non approval
MAH Transfer CRN009JLY	SmPC section 7, 8, 10 Package Leaflet New MA Holder: Clonmel Healthcare Ltd, New PA number: PA0126/330/001	N/A	04/12/2020	Approved 04/12/2020