IPAR

Health Products Regulatory Authority

PUBLIC ASSESSMENT REPORT FOR A MEDICINAL PRODUCT FOR HUMAN USE

Scientific discussion

Strepsils Intensive Orange Sugar Free 8.75mg Lozenges
Flurbiprofen
PA 0979/041/004

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 Strepsils Intensive Orange Sugar free 8.75mg Lozenges, from Reckitt Benckiser Ireland Ltd. on 4th July 2014 for the symptomatic relief of sore throats.

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

Name of the product	Strepsils Intensive Orange Sugar Free
Name(s) of the active substance(s) (INN)	Flurbiprofen
Pharmacotherapeutic classification (ATC code)	R02A
Pharmaceutical form and strength(s)	8.75mg Lozenges
Marketing Authorisation Number(s) in Ireland (PA)	PA 0979/041/004
Marketing Authorisation Holder	Reckitt Benckiser Ireland Ltd

II QUALITY ASPECTS

II.3 Medicinal product

P.1 Composition

The finished product is a 2.6g circular, intagliated, pale orange coloured, high-boiled lozenge, which contains flurbiprofen 8.75mg as active ingredient. The lozenge has a characteristic taste of orange and is sugar free.
Other excipients include macrogol 300, potassium hydroxide, orange flavour, levomenthol, acesulfame potassium, FD & C yellow No. 6 colour, liquid maltitol and isomalt.

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)

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 oromucosal preparations, 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 product is presented as blisters consisting of opaque PVC coated with PVdC with aluminium lidding.

Evidence has been provided that the blisters comply 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 demonstrating the stability of the product for 2 years when stored below 25°C and in the original package in order to protect from moisture.

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 Strepsils Intensive Orange Sugar Free 8.75mg Lozenges.

III NON-CLINICAL ASPECTS

III.1 Introduction

This active substance has been available on the European/Irish market for a number years. Preclinical data have been superseded by clinical experience and therefore no preclinical assessment report is available.

HPRA has been assured the GLP standards were followed in an appropriate manner in the studies conducted.

III.2 Pharmacology

The principal pharmacological mode of action of flurbiprofen, like those of other NSAIDs, is the inhibition of prostaglandin synthesis by cyclooxygenase (COX; PGH2 synthase) from arachidonic acid.

COX exists as two distinct isozymes, the constitutive form COX-1, responsible for prostaglandin biosynthesis under normal circumstances and COX-2, which is induced by the inflammatory process itself and thought to mediate inflammation.

Flurbiprofen is a potent inhibitor of both COX-1 and COX-2 in vitro and has COX-1/COX-2 ratio of 1.3, which compares well with those of relatively well tolerated NSAIDs such as diclofenac (ratio of 0.7) and naproxen (ratio of 0.6).

R- and S-flurbiprofen have independent pharmacological activities; the S-enantiomer is an analgesic, antipyretic and anti-inflammatory as a result of COX inhibition, while both the S and R-forms may act as analgesics via a central mechanism.

Although R-flurbiprofen does not inhibit COX activity in vitro, it has marked antinociceptive and anti-inflammatory activity. R-Flurbiprofen has marked central analgesic activity, potentially by the effect upon endogenous cannabinoids . The anti-inflammatory activity of flurbiprofen is comparable with that of dexamethasone and a number of lines of evidence suggest that inhibition of NF-B activation is responsible. Both enantiomers of flurbiprofen have this activity

but the R-enantiomer is more potent than the S-enantiomer.

III.3 Pharmacokinetics

The pharmacokinetic profile of flurbiprofen is well characterised in multiple species (including man) and existing preclinical pharmacokinetic studies contribute insight into the time course and movement of flurbiprofen into, through, and out of the body.

Flurbiprofen is extensively and non-stereospecifically absorbed in multiple species following oral route exposure (>97%), with peak plasma concentrations occurring between 45 and 90 minutes, depending on the species. Flurbiprofen is distributed extravascularly, but has a small volume of distribution due to its extensive binding to plasma proteins (primarily albumin).
Flurbiprofen is primarily cleared by the liver, and is metabolised via Phase I (hydroxylation) and Phase II (glucuronidation) enzymes.

Elimination of an oral dose occurs mainly via urine as metabolites (approximately 90% of an oral dose) and unchanged flurbiprofen (remainder), with minimal biliary excretion and no bioaccumulation. The elimination half-life of flurbiprofen varies among species, and ranges from three to eight hours for a single dose.

III.4 Toxicology

In rats exposed to 0.4 mg/Kg/day and above during pregnancy an increased incidence of stillborn pregnancy has been observed. However, the relevance of this fact to humans is doubtful and not reflected in human experience with flurbiprofen so far.

III.5 Ecotoxicity/environmental risk assessment

N/A

III.6 Discussion on the non-clinical aspects

These active substances are the same as those present in ‘Strepsils intensive 8.75 Lozenges’on the European market PA 979/41/1. No new preclinical data have been submitted. As such, no pre-clinical assessment has been made on the application.

IV CLINICAL ASPECTS

IV.1 Introduction

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

Flurbiprofen is a non-steroidal antiinflammatory drug which has potent analgesic, antipyretic and antiinflammatory properties which are thought to result from the drug’s ability to inhibit prostaglandin synthesis.

The content of the SPC approved during the national procedure is in accordance with that accepted for the reference product Strepsils intensive 8.75 Lozenges’on the European market PA 979/41/1 marketed by MAH.

The applicant has submitted a number of clinical studies to assess dose, efficacy, tolerability and safety of the flurbiprofen lozenge in the short-term relief of sore throat.

Efficacy studies included in the clinical programme
Two dose ranging studies: BH5007 (Schachtel et al 2002) and BH5008, which compared the efficacy of 2.5 mg, 5 mg and 12.5 mg flurbiprofen lozenges to placebo. Three efficacy studies: BH5009 (Benrimoj et al 2001), TH9616 (Watson et al 2000) and TH9722 (Blagden et al 2002), which assessed the efficacy of flurbiprofen 8.75 mg lozenge.
A positive comparator study: TH0504, which compared the efficacy and duration of action of flurbiprofen 8.75 mg lozenge to benzydamine hydrochloride 3 mg lozenge.
An exploratory study: TH0612, which investigated whether the 2-stopwatch technique was appropriate for assessing

onset of efficacy in sore throat.
A post-marketing surveillance study for Germany: Ramge 2003 (Anon 2004), which assessed the efficacy and safety of flurbiprofen 8.75 mg lozenge as a multiple dose treatment.

Design of studies
Studies BH5007, BH5008, BH5009, TH9616 and TH9722 were randomised, doubleblind, placebo-controlled, parallel group, multiple dose studies in adult patients with sore throat due to an upper respiratory infection.
TH0504 was a single-blind comparative single dose study.
TH0612 was an exploratory, open, active comparator study.

The post-marketing surveillance study (Ramge 2003) was an open-label study.
Studies BH5007, BH5008, BH5009, TH9616 and TH9722 all used identical efficacy variables, i.e. subjective measurement of pain relief and change in absolute throat soreness.
Studies BH5009, TH9616 and TH9722 included 'Flurbiprofen 8.75 mg lozenge'. In addition, the active-comparator study (TH0504) and the open-label post-marketing surveillance study (Ramge 2003) also investigated the efficacy of 'Flurbiprofen 8.75 mg lozenge'. The latter studies used different inclusion criteria and efficacy variables.
The Applicant conducted a meta-analysis according to a pre-defined protocol using efficacy data from studies BH5007, BH5008, BH5009, TH9616 and TH9722.

In summary, symptomatic relief of sore throat was evident from all the studies conducted todate.

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

IV.2 Pharmacokinetics

Flurbiprofen is rapidly absorbed following the use of Flurbiprofen Lozenges with plasma concentrations peaking at 30 – 40 minutes. Peak concentrations are achieved more rapidly than, but are of similar magnitude to, those achieved after an equivalent swallowed dose.

Flurbiprofen is rapidly distributed throughout the body. It is mainly metabolised by hydroxylation and excreted via the kidneys.

It is extensively bound to plasma proteins and has an elimination half-life of 3 to 6 hours.

The duration of effect for the flurbiprofen lozenge is over 6 hours with reduction in throat soreness maintained up to 4 hours.

Flurbiprofen is excreted in very small amounts in human milk (less than 0.05 μg/ml).

IV.3 Pharmacodynamics

Flurbiprofen is a non-steroidal antiinflammatory drug which has potent analgesic, antipyretic and antiinflammatory properties which are thought to result from the drug's ability to inhibit prostaglandin synthesis.

<u>Distribution</u>
Flurbiprofen is rapidly distributed throughout the body and is extensively bound to plasma proteins.

<u>Metabolism/Excretion</u>
Flurbiprofen is mainly metabolised by hydroxylation and excreted via the kidneys. It has an elimination half-life of 3 to 6 hours. Flurbiprofen is excreted in very small amounts in human milk (less than 0.05ug/ml). Approximately 20-25% of a flurbiprofen oral dose is excreted unchanged.

<u>Special Groups</u>
No difference in pharmacokinetic parameters between elderly and young adults volunteers has been reported following oral administration of flurbiprofen tablets. No pharmacokinetic data have been generated in children below 12 years of age following administration of Flurbiprofen 8.75 mg however administration of both flurbiprofen syrup and

suppository formulations indicate no significant differences in pharmacokinetic parameters compared with adults.

IV.4 Clinical Efficacy

Efficacy has been demonstrated in clinical trials mentioned above.

IV.5 Clinical Safety

Flurbiprofen is a non-steroidal antiinflammatory drug which has potent analgesic, antipyretic and antiinflammatory properties which are thought to result from the drug's ability to inhibit prostaglandin synthesis.

The safety profile is well characterised andexpected adverse reactions are listed in section 4.8 of the SPC.

This product will reuire a renewal 5 years after authorisation date, thereafter the schedule for Periodic Safety Update Reports (PSUR) will be submitted every three years in accordance with EU timeline.

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 active component Flurbiprofen is ell known and its safety profile is well characterised.
The SPC and patient leaflet are in line with the MAHs authorised similar products i.e.
Strepsils intensive 8.75 lozenges PA 979/41/1, Strepsils intensive 8.75 granules PA 979/41/2 and Strepsils intensive 8.75 mint granules PA 979/41/3.

V OVERALL CONCLUSIONS

The overall assessment outcome of Strepsils Intensive Orange Sugar Free 8.75mg Lozenges is positive.

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

The IMB, on the basis of the data submitted, considered that Strepsils Intensive Orange Sugar Free 8.75mg Lozenges demonstrated adequate evidence of efficacy for the approved indication(s) as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.