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 (formerly the IMB) granted a marketing authorisation for Advil Cold & Flu Coated Tablets, from Pfizer Healthcare Ireland on 8th September 1994 for the symptomatic relief of the symptoms associated with the common cold and influenza including blocked sinuses.

This assessment report concerns the MR-procedure IE/H/420/001/MR (Advil Cold & Flu 200/30 Coated Tablets), with Ireland acting as Reference Member State. Concerned Member States are: UK, BE, PL, HU, SK and CZ. This application is made according to Article 10(b) of the EU-Directive 2001/83/EC, a fixed combination application.

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:
Name(s) of the active substance(s) (INN):
Pharmacotherapeutic classification (ATC code)
Pharmaceutical form and strength(s):
Marketing Authorisation Number(s) in Ireland:
Marketing Authorisation Holder:
MRP/DCP No.
Reference Member State:
Concerned Member State:
Advil Cold & Flu Coated Tablets
Ibuprofen 200mg
Pseudoephedrine Hydrochloride 30mg
Ibuprofen and pseudoephedrine
Propionic acid derivatives ATC code M01AE51
Coated tablets
ibuprofen 200mg
pseudophedrine hydrochloride 30mg
(PA) 0822/164/001

Pfizer Healthcare Ireland
IE/H/420/001/MR
IE
UK, PL, HU, SK, CZ, BE, LU

II. QUALITY ASPECTS

II.1. Introduction

This application is for Advil Cold & Flu coated tablets, Ibuprofen 200mg Pseudoephedrine Hydrochloride 30mg.

II.2 Drug substance

The active substances are Ibuprofen and Pseudoephedrine Hydrochloride, both established active substances described in the European Pharmacopoeia, and are manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specifications for both actives are considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided in respect of each active.

II.3 Medicinal product

P.1 Composition

Active Substances	mg/tablet
Ibuprofen	200
Pseudoephedrine Hydrochloride	30

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 tablets, 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 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 Advil Cold & Flu coated tablets, Ibuprofen 200mg Pseudoephedrine Hydrochloride 30mg.

III. NON-CLINICAL ASPECTS

The pharmacodynamic, pharmacokinetic and toxicological properties of both ibuprofen and pseudoephedrine hydrochloride are well known. As ibuprofen and pseudoephedrine hydrochloride are widely used, well-known active substances, the applicant has not provided additional studies and further studies are not required.

Since ibuprofen and pseudoephedrine hydrochloride 200/30 mg coated tablets are intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

IV. CLINICAL ASPECTS

IV.1 Introduction

Ibuprofen and pseudoephedrine hydrochloride are well known active substances with established efficacy and tolerability.

A national marketing authorisation for Advil Cold & Flu Coated Tablets was granted in Ireland on 08 September 1994. This was an application under Article 4.8(b) of Directive 65/65/EEC as a new combination of existing substances. The national license number is PA 0822/164/001.

This fixed-combination product corresponds closely to combinations that are already in widespread use. In support of this bibliographic marketing authorisation application, a critical analysis of a world-wide literature search for review articles and publications defining the pharmacodynamics, pharmacokinetics and publications to support the efficacy and safety of ibuprofen and pseudoephedrine in the proposed indication was provided. Furthermore, bioequivalence and clinical efficacy and safety studies conducted specifically for the ibuprofen/pseudoehedrine combination were provided.

The objective of bioequivalence study WM-418 was twofold: first, to verify that capsules containing ibuprofen 200 mg and pseudoephedrine 30 mg used in clinical studies were bioequivalent to both reference products (Advil and Sudafed) given simultaneously; secondly, to verify that the marketed formulation, Advil Cold & Flu Coated Tablets, was bioequivalent to the capsules for use in clinical studies. The 90% confidence interval for the test/reference ratio for Cmax and AUC for both ibuprofen and pseudoephedrine was contained within the accepted range of 80%-125% and bioequivalence has been shown.

The above study is supportive and not pivotal to this application and is acceptable.

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

IV.2 Pharmacokinetics

The pharmacokinetics of ibuprofen and pseudoephedrine individually are well known.

In adults, ibuprofen from solid oral dosing is absorbed from the gastrointestinal tract and peak plasma concentrations occur about 1 to 2 hours after ingestion. Ibuprofen is primarily metabolised in the liver to 2-Hydroxyibuprofen and 2-carboxyibuprofen. Ibuprofen is 90 to 99% bound to plasma proteins and has a plasma half-life of about 2 hours. It is rapidly excreted in the urine mainly as metabolites and their conjugates. About 1% is excreted in the urine as unchanged ibuprofen and about 14% as conjugated ibuprofen.

Pseudoephedrine Hydrochloride is rapidly absorbed from the gastro-intestinal tract with peak plasma levels at 1-3 hours. It is partly metabolised in the liver like most sympathomimetics, but is mainly excreted unchanged in the urine.
In support of this application, study 416 was also submitted. This study examines to see if there is any interaction between ibuprofen and pseudoephedrine when the two drugs are given concomitantly. It was concluded that there was no pharmacokinetic interaction in terms of either the rate or the extent of absorption of ibuprofen and pseudoephedrine when administered simultaneously compared to separate administration.

IV.3 Pharmacodynamics

Ibuprofen is a non steroidal anti-inflammatory agent belonging to the propionic acid class of drugs. It has analgesic, antipyretic and anti-inflammatory properties.
Pseudoephedrine Hydrochloride is a sympathomimetic agent which causes vasoconstriction of nasal mucosa, thereby reducing rhinorrhoea and nasal congestion.

IV.4 Clinical Efficacy

Ibuprofen, a propionic acid, non-steroidal anti-inflammatory drug, is effective at OTC doses in the treatment of symptoms associated with the common cold, such as fever, sore throat, pain myalgia, headache, sinus pains, chills and malaise. Pseudoephedrine, a stereoisomer of ephedrine, has a good efficacy record as a nasal decongestant supported by clinical trials. Controlled clinical studies versus placebo and/or reference products have demonstrated the efficacy of this combination in nasal congestion and for symptoms of acute rhinosinusitis with nasal congestion, headache and/or fever. The clinical efficacy of IBU/PSE combination in treating nasal congestion was demonstrated by objective and subjective criteria during four double-blind, randomized, comparative studies versus placebo or reference products conducted in a total of 1456 patients. The efficacy of ibuprofen/pseudoephedrine at 200/30 mg and 400/60 mg doses has been shown for relieving nasal congestion due to upper respiratory tract infection and allergic rhinitis. In one study (WM-442), a clear dose-response was demonstrated between single doses of 1 and 2 capsules of ibuprofen/pseudoephedrine combination. In another study (WM-446), the results demonstrated that the ibuprofen/pseudoephedrine combination at two dose levels (200/30 mg and 400/60 mg) were effective in relieving nasal congestion in subjects with allergic rhinitis.
For bioequivalence of the ibuprofen/pseudoephedrine capsules used in these studies to ibuprofen and pseudoephedrine coated tablets, the applicant has submitted a bioequivalence study (Study WM-418).
The body of evidence from the literature together with the bioequivalence study and experience of the established use of this drug combination provide reassurance for its effective use for the given indications.

The content of the SmPC approved during this procedure is in line with similar products licensed in the EU. The MAH has committed to updating the national product information following comments from the RMS and CMS during the procedure.

IV.5 Clinical Safety

Ibuprofen:
Ibuprofen is an established analgesic with a known safety profile.
Pseudoephedrine:
Pseudoephedrine has a good safety record. Many millions of patients are exposed to PSE in common cold medicines each year, as it is found in numerous common cold and cough medicines.
IBU/PSE combination:
Safety data from post-marketing experience are included and analyzed in regular PSURs.
Much is known about the clinical safety of ibuprofen/pseudoephedrine from clinical trials and post-marketing surveillance.
Any known potential risks are controlled by listing in the Summary of Product Characteristics.
The marketing authorisation holder (MAH) has submitted a summary of 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.

Risk Management Plan

The Applicant has confirmed that they will submit an updated Risk Management Plan in the new RMP format as committed during the MR procedure IE/0420/001/MR, as a post approval variation to all CMS concerned in the procedure.

The updated RMP will take into account the additions and changes requested by the CMS and RMS as committed to during the MR procedure.

The following has been agreed during this procedure.

Important identified risks, potential risks and important interactions:
1. The applicant has agreed to include gastro-intestinal ulceration (including perforation) and haemorrhage as important identified risks.
2. With regard to the interaction with MAOIs, the applicant has agreed to include this under Part II Module SVII.4.2 of the RMP.
3. With regard to interaction with tricyclic antidepressants, the applicant has agreed to include this under Part II Module SVII.4.2 of the RMP.
4. With regard to interaction with NSAIDs, the MAA has agreed to include this under Part II Module SVII.4.2 of the RMP.
5. In light of the specific risk of bronchospasm with this medication in particular patient groups, the applicant has agreed to highlight this risk specifically under the hypersensitivity identified risk. (please see proposed title of risk under point 8 below).
6. The applicant agrees to include cardiovascular disorders as an important identified risk in the RMP.
7. The applicant has agreed to include “use in last trimester of pregnancy” instead of “use in late pregnancy” as an important identified risk.
8. Due to the similar mechanism of action and in most cases representing different stages of spectrum of the same medical concept, the applicant proposes to include serious skin reactions in the title of Hypersensitivity reactions but to clearly specify it out to read: “hypersensitivity reactions (including serious skin reactions such as exfoliative dermatitis, Stevens Johnson syndrome (SJS) and toxic epidermal necrosis (TEN), and including bronchospasm particularly in those patients with a history of bronchial asthma or allergic disease)”
9. The applicant agrees to include hypersensitivity reactions as an important identified risk in the updated RMP and will include conditions such as anaphylactic reaction, angioedema, allergic conditions, as well as the previously discussed bronchospasm (in patients with asthma or allergic disease), and severe cutaneous adverse reactions due to similar mechanisms.
10. Off-label use in children aged <12 years: although labelling reduces this risk (see section 4.2. of the SmPC), this risk cannot be completely ruled out. The applicant agrees to add off label use in children aged <12 as an important potential risk.
11. The applicant agrees to include impaired female fertility under important potential risks.

Missing Information:
1. Use in breastfeeding women: no safety data in breast-fed infants (see section 4.6. of the SmPC)

A variation to update the RMP should be submitted within 3 months of the closure of the above mentioned MR Procedure.

Periodic Safety Update Reports (PSUR) submission:

Currently the fixed dose combination (FDC) ibuprofen/pseudoephedrine is reflected in the PSUR WS List, and is included with a 1 yearly frequency, a frequency that was agreed in the frame of the EURD list.

The applicant proposes to submit the PSUR in line with their current French MRP license FR/H/0238/001/MR, on the 26th of September 2014, a submission date of DLP + 70.

February 2016: Variation approved to implement Article 31 referral product information wording recommended by Pharmacovigilance Risk Assessment Committee (PRAC) which was published in May 2015. The revised wording provided advice on the cardiovascular risk of high-dose ibuprofen along with information on the interaction between ibuprofen and aspirin. The updates were to sections 4.2, 4.3, 4.4, 4.5, 4.8 and 5.1 of the SmPC and to the PL.

IV.6 Discussion on the clinical aspects

Advil Cold & Flu Coated Tablets have been marketed in Ireland since 1994. The efficacy and safety profile is well-established.

V. OVERALL CONCLUSIONS

Ibuprofen and pseudoephedrine hydrochloride are well known active substances with established efficacy and tolerability. This fixed-combination product corresponds closely to combinations that are already in widespread use.

The content of the SmPC approved during this procedure is in line with similar products licensed in the EU. The MAH has committed to updating the national product information following comments from the RMS and CMS during the procedure.

The applicant has confirmed that they will submit an updated risk management plan (RMP) in the new RMP format as committed during the MR procedure IE/0420/001/MR, as a post approval variation to all CMS concerned in the procedure.

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 Advil Cold & Flu Coated Tablets demonstrated adequate evidence of efficacy for the approved indications as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

October 2020

VII. UPDATES

Scope
To update the SmPC and PL in line with the PRAC Article 31 referral recommendations on ibuprofen published in May 2015

Procedure number	Product Information affected	Date of start of procedure	Date of end of procedure	Approval/non approval
IE/H/0420/001/IB/007 CRN2163665	SmPC section 4.2, 4.3, 4.4, 4.5, 4.8 and 5.1. Package Leaflet	16/10/2015	15/02/2016	Approved

Procedure number	Product Information affected	Date of start of procedure	Date of end of procedure	Approval/non approval
MAH Transfer CRN009XY4	SmPC section 7, 8, 10 Package Leaflet New MA Holder: GlaxoSmithKlineConsumer Healthcare (Ireland) Limited New PA number: PA0678/147/001	N/A	30/10/2020	Approved 30/10/2020