IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Brupro Cold & Flu 200 mg/30 mg film-coated tablets
Ibuprofen
Pseudoephedrine hydrochloride
PA0074/067/006

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.

CONTENTS

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Brupro Cold & Flu 200mg/30mg film-coated tablets from Rowa Pharmaceuticals Limited on 30th April 2021.

For the Symptomatic relief of nasal/sinus congestion with headache, fever and pain associated with the common cold and flu. Brupro Cold & Flu is indicated in adults and adolescents aged 12 years and older.

This new national application concerns a generic application of a fixed combination of 200 mg ibuprofen and 30 mg pseudoephedrine submitted under Article 10(1) of Directive 2001/83 EC, as amended.

In this assessment report, the name Brupro Cold & Flu 200mg/30mg film-coated tablets is used. Each film-coated tablet contains 200 mg ibuprofen and 30 mg pseudoephedrine hydrochloride.

The reference medicinal product is Advil Cold and Flu 200mg/30mg (Pfizer) PA 0822/164/001 authorised in Ireland 1994-09-08.

The originator product has been authorized in the EEA for more than 10 years, thus the period of data exclusivity has expired. No new clinical efficacy studies were conducted for this application, which is acceptable given that the application is for a generic version of a product that has been licensed for over 20 years.

This same generic version of Ibuprofen/Pseudoephedrine hydrochloride has been subject of a DCP procedure. Ibuprofen/Pseudoephedrine Hydrochloride - 200/30mg - DCP: DE/H/4182/001/DC. By way of this DCP a national marketing authorisation was granted in IE on 29/01/2016 (PA1958/005/001 transfer to PA 0823/067/001)

This product will be subject to non- prescription pharmacy only sale.

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	Brupro Cold & Flu 200 mg/30 mg film-coated tablets
Name(s) of the active substance(s) (INN)	Ibuprofen Pseudoephedrine hydrochloride
Pharmacotherapeutic classification (ATC Code)	R05X
Pharmaceutical form and strength(s)	200, mg, Film-coated tablet 30, mg, Film-coated tablet
Marketing Authorisation Number(s) in Ireland (PA)	PA0074/067/006
Marketing Authorisation Holder	Rowa Pharmaceuticals Limited Newtown Bantry Co. Cork Ireland

II. QUALITY ASPECTS

II.1. Introduction

This application is for Brupro Cold & Flu 200mg/30mg film-coated tablets.

II.2 Drug substance

The active substances are Ibuprofen and Pseudoephedrine Hydrochloride, established active substances described in the European Pharmacopoeia, and are 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.

Biological products – reference to Plasma Master File/ Vaccine Antigen Master File.

II.3 Medicinal product

P.1 Composition

Composition of the medicinal product (quantity of active, dilution for homeopathics).

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 the dosage form, 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 Brupro Cold & Flu 200mg/30mg film-coated tablets.

III. NON-CLINICAL ASPECTS

This active substance is a generic formulation of Advil Cold & Flu Coated Tablets Ibuprofen 200mg Pseudoephedrine Hydrochloride 30mg 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.

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 of toxicity to aquatic organisms is identified for ibuprofen and instructions for disposal of unused medicine are included in the product information.

IV. CLINICAL ASPECTS

IV.1 Introduction

Ibuprofen/Pseudoephedrine hydrochloride are well known active substance with established efficacy and tolerability.

The content of the SmPC approved during this national procedure is in accordance with that accepted for the reference product Advil Cold and Flu tablets marketed by Pfizer.

For this generic application, the applicant has submitted one bioequivalence study

report, a randomized, single-dose, two treatment, two-period, two-sequence, crossover, comparative bioavailability of two formulations of Ibuprofen and Pseudoephedrine Hydrochloride 200 mg/30 mg Tablets under fasting conditions in which the pharmacokinetic profile of the test product Ibuprofen/Pseudoephedrine HCl 200/30 mg Film-Coated Tablets is compared with the pharmacokinetic profile of the reference product RhinAdvil Rhume 200 mg/30 mg Film-Coated Tablets.

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

IV.2 Pharmacokinetics

Ibuprofen/Pseudoephedrine hydrochloride are widely used, well-known active substances, the pharmacokinetic properties of the active are well known. The applicant has not provided additional studies and further studies are not required. The submitted overview based on literature review is, thus, appropriate.

Ibuprofen

Ibuprofen is rapidly absorbed from the gastrointestinal tract, and its plasma concentrations reach a maximum peak level about 2 hours after administration. Elimination half-life is approximately 2 hours.

Ibuprofen is metabolised in the liver into two major inactive metabolites and these together with unchanged ibuprofen are excreted by the kidney either as such or as conjugates. Excretion by the kidney is both rapid and complete.

Ibuprofen is extensively bound to plasma proteins.

Pseudoephedrine

Pseudoephedrine is absorbed in the gastrointestinal tract and is largely excreted in the urine unchanged, together with small amounts of a hepatic metabolite.

It has an elimination half-life of several hours, which may be reduced by acidifying the urine.

IV.3 Pharmacodynamics

No new studies on pharmacodymanics have been submitted and this is acceptable for a generic application. The submitted overview based on literature review is, thus, appropriate.

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

Pseudoephedrine hydrochloride is a sympathomimetic agent, which acts as a nasal decongestant when used by systemic route.

IV.4 Clinical Efficacy

Ibuprofen/Pseudoephedrine Hydrochloride 200/30mg is a well-known medicinal product with an established favourable efficacy profile. A detailed clinical overview on efficacy has been submitted.
Apart from a single BE study, and a pilot BE study the applicant has not provided additional clinical studies and further studies are not required.

IV.5 Clinical Safety

Ibuprofen/Pseudoephedrine Hydrochloride 200/30mg is a well-known medicinal product with an established favourable safety profile.

Any known potential risks are listed in the Summary of Product Characteristics (SmPC)

For full safety prescribing information please see the SmPC for Brupro Cold & Flu 200mg/30mg film-coated tablets.

Risk Management Plan

Risk Management Plan version 0.1, with date of final sign off 19 June 2020 is considered acceptable. The approved summary of safety concerns is outlined below:

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

Routine pharmacovigilance and routine risk minimisation measures are proposed and this is considered acceptable.

Periodic Safety Update Report (PSUR):

The PSURs should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided under Article 107c (7) of Directive 2001/83/EC and published on the European medicines web-portal.

IV.6 Discussion on the clinical aspects

This application concerns an Article 10(1) generic version of Ibuprofen/Pseudoephedrine Hydrochloride 200/30mg, such abridged applications avoid the need for repetitive tests on humans. In line with the requirements for an Article 10(1) application, a BE study has been presented in the dossier to demonstrate bioequivalence between the test and the designated reference product

The study design is in line with the requirements set out in Guideline on the investigation of Bioequivalence CPMP/EWP/QWP/1401/98 and is acceptable.
The study population is considered appropriate and suitable randomisation tables have been presented. The sampling scheme, period and washout are suitable, the analytical method is acceptable.Pharmacokinetic variables are appropriate as are the method of assessment of pharmacokinetic parameters. The statistics are adequately described and the methods are acceptable.

The results show that the 90% confidence intervals of the relative mean (1S, 2S)-Pseudoephedrine and (S)-Ibuprofen AUC_t and C_{max} of the test to reference products are within the 80.00-125.00% range.
Therefore, it could be concluded that the test product Ibuprofen/Pseudoephedrine HCl 200/30 mg Film-Coated Tablets (Swiss Caps AG, Switzerland) exhibits an equivalent rate and extent of absorption to the reference product RhinAdvil Rhume 200

mg/30 mg Film-Coated Tablets (Wyeth Santé Familiale, France) in healthy subjects after a single, oral dose, under fasting conditions and fulfils the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

V. OVERALL CONCLUSIONS

Ibuprofen/Pseudoephedrine Hydrochloride 200/30mg tablets is a generic form of Advil Cold and Flu 200mg/30mg tablets.

Advil Cold and Flu 200mg/30mg tablets 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 is 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.

The HPRA, on the basis of the data submitted considered that Ibuprofen/Pseudoephedrine Hydrochloride 200/30mg tablets mg demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE