IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Apremilast axunio Pharma 30 mg film-coated tablets
Apremilast
PA23438/003/002

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 Apremilast axunio 30 mg film-coated tablets, from Axunio Pharma GmbH
on 7th November 2025 for

Psoriatic arthritis
Alone or in combination with Disease Modifying Antirheumatic Drugs (DMARDs), is indicated for the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant to a prior DMARD therapy (see section 5.1).

Psoriasis
Indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or psoralen and ultraviolet-A light (PUVA).

Behçet's disease
Indicated for the treatment of adult patients with oral ulcers associated with Behçet's disease (BD) who are candidates for systemic therapy.

One application for marketing authorisation has been submitted under Article 10(1) of Directive 2001/83/EC. In this decentralised procedure, Ireland (IE) is the reference member state and the concerned member states (CMS) are as follows:

IE/H/1398/001-002/DC: DE
The reference product was Otezla 10 mg, 20 mg and 30 mg film-coated tablets MAH: Amgen Europe B.V.

The product is subject to medical prescription, which may not be renewed.

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	Apremilast axunio Pharma 30 mg film-coated tablets.
Name of the active substance(s) (INN)	Apremilast
Pharmacotherapeutic classification (ATC code)	L04AA32
Pharmaceutical form and strength(s)	30 mg Film-coated tablet
Marketing Authorisation Number(s) in Ireland (PA)	PA23438/003/002
Marketing Authorisation Holder	axunio Pharma GmbH
MRP/DCP No.	IE/H/1398/002/DC
Reference Member State	IE
Concerned Member State	DE

II. QUALITY ASPECTS

II.1. Introduction
This application is for Apremilast 30mg film coated tablets.

II.2 Drug substance
The active substance is apremilast, an established active substance not 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 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 film-coated 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 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 have been provided, assuring consistent quality of Apremilast 30mg film-coated tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is the same as that present in Otezla (10 mg, 20 mg and 30 mg film-coated tablets) on the European market since 2015. 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.

The pharmacodynamic, pharmacokinetic and toxicological properties of apremilast are well known.

III.2 Pharmacology

N/A

III.3 Pharmacokinetics

N/A

III.4 Toxicology

N/A

III.5 Ecotoxicity/environmental risk assessment

Since Apremilast axunio (10 mg, 20 mg and 30 mg film-coated tablets) is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

The pharmacodynamic, pharmacokinetic and toxicological properties of apremilast are well known. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology provided is adequate. As apremilast is a widely used, well-known active substance, the applicant has not provided additional studies, and further studies are not required. Non-clinical findings are adequately represented in the appropriate sections of the SmPC.

IV. CLINICAL ASPECTS

IV.1 Introduction

This is a generic application submitted under article 10(1) of Directive 2001/83/EC.

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

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Otezla 10 mg, 20 mg and 30 mg film-coated tablets (EU/1/14/981/001-003), MAH: Amgen Europe BV.

For this generic application, the applicant has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Apremilast 30 mg film-coated tablets of axunio is compared with the pharmacokinetic profile of the reference product Otezla 30 mg film-coated tablets of Amgen Europe B.V. Minervum 7061, 4817 ZK Breda, Netherlands.

An open label, balanced, randomised, two-treatment, two-sequence, two-period, single dose, crossover, oral bioequivalence study was carried out.

Apremilast 30 mg film-coated tablets of axunio was compared with the pharmacokinetic profile of the reference product Otezla 30 mg film-coated tablets of Amgen Europe B.V. Minervum 7061, 4817 ZK Breda, The Netherlands. Based on the pharmacokinetic parameters of active substance, the reference tablet Otezla 30 mg film-coated tablets marketed by Amgen Europe B.V. and test tablet Apremilast 30 mg film-coated tablets are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

A biowaiver is applied for Apremilast 10 mg and 20 mg film-coated tablets. Apremilast 10 mg and 20 mg film-coated tablets are dose proportional with the 30mg strength. The pharmacokinetics of the active substance are linear. The results of the bioequivalence study performed with the 30mg film-coated tablets therefore apply to the other strengths.

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

IV.2 Pharmacokinetics

Absorption

Apremilast is well absorbed with an absolute oral bioavailability of approximately 73%, with peak plasma concentrations (Cmax) occurring at a median time (tmax) of approximately 2.5 hours. Apremilast pharmacokinetics are linear, with a dose-proportional increase in systemic exposure in the dose range of 10 to 100 mg daily. Accumulation is minimal when apremilast is administered once daily and approximately 53% in healthy subjects and 68% in patients with psoriasis when administered twice daily. Co-administration with food does not alter the bioavailability, therefore, apremilast can be administered with or without food.

Distribution

Human plasma protein binding of apremilast is approximately 68%. The mean apparent volume of distribution (Vd) is 87 L, indicative of extravascular distribution.

Biotransformation

Apremilast is extensively metabolised by both CYP and non-CYP mediated pathways including oxidation, hydrolysis, and conjugation, suggesting inhibition of a single clearance pathway is not likely to cause a marked drug-drug interaction. Oxidative metabolism of apremilast is primarily mediated by CYP3A4, with minor contributions from CYP1A2 and CYP2A6. Apremilast is the major circulating component following oral administration. Apremilast undergoes extensive metabolism with only 3% and 7% of the administered parent compound recovered in urine and faeces, respectively. The major circulating inactive metabolite is the glucuronide conjugate of O-demethylated apremilast (M12). Consistent with apremilast being a substrate of CYP3A4, apremilast exposure is decreased when administered concomitantly with rifampicin, a strong inducer of CYP3A4. In vitro, apremilast is not an inhibitor or inducer of cytochrome P450 enzymes. Hence, apremilast coadministered with substrates of CYP enzymes is unlikely to affect the clearance and exposure of active substances that are metabolised by CYP enzymes. In vitro, apremilast is a substrate, and a weak inhibitor of P-glycoprotein (IC50 > 50 μM), however clinically relevant drug interactions mediated via P-gp are not expected to occur. In vitro, apremilast has little to no inhibitory effect (IC50 > 10 μM) on Organic Anion Transporter (OAT)1 and OAT3, Organic Cation Transporter (OCT)2, Organic Anion Transporting Polypeptide (OATP)1B1 and OATP1B3, or breast cancer resistance protein (BCRP) and is not a substrate for these transporters. Hence, clinically relevant drug-drug interactions are unlikely when apremilast is coadministered with drugs that are substrates or inhibitors of these transporters.

Elimination

The plasma clearance of apremilast is on average about 10 L/hr in healthy subjects, with a terminal elimination half-life of approximately 9 hours. Following oral administration of radiolabelled apremilast, about 58% and 39% of the radioactivity is recovered in urine and faeces, respectively, with about 3% and 7% of the radioactive dose recovered as apremilast in urine and faeces, respectively

Elderly patients

Apremilast was studied in young and elderly healthy subjects. The exposure in elderly subjects (65 to 85 years of age) is about 13% higher in AUC and about 6% higher in Cmax for apremilast than that in young subjects (18 to 55 years of age). There is limited pharmacokinetic data in subjects over 75 years of age in clinical trials. No dosage adjustment is necessary for elderly patients.

Renal impairment

There is no meaningful difference in the PK of apremilast between mild or moderate renally impaired subjects and matched healthy subjects (N = 8 each). The results support that no dose adjustment is needed in patients with mild and moderate renal impairment. Apremilast dose should be reduced to 30 mg once daily in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m2 or CLcr < 30 mL/min). In 8 subjects with severe renal impairment to whom a single dose of 30 mg apremilast was administered, the AUC and Cmax of apremilast increased by approximately 89% and 42%, respectively.

Hepatic impairment

The pharmacokinetics of apremilast and its major metabolite M12 are not affected by moderate or severe hepatic impairment. No dose adjustment is necessary for patients with hepatic impairment.

IV.3 Pharmacodynamics

Pharmacotherapeutic group: Immunosuppressants, selective immunosuppressants.
ATC code: L04AA32

Mechanism of action

Apremilast, an oral small-molecule inhibitor of phosphodiesterase 4 (PDE4), works intracellularly to modulate a network of pro-inflammatory and anti-inflammatory mediators. PDE4 is a cyclic adenosine monophosphate (cAMP)-specific PDE and the dominant PDE in inflammatory cells. PDE4 inhibition elevates intracellular cAMP levels, which in turn down-regulates the inflammatory response by modulating the expression of TNF-α, IL-23, IL-17 and other inflammatory cytokines. Cyclic AMP also modulates levels of anti-inflammatory cytokines such as IL-10. These pro- and anti-inflammatory mediators have been implicated in psoriatic arthritis and psoriasis.

Pharmacodynamic effects

In clinical studies in patients with psoriatic arthritis, apremilast significantly modulated, but did not fully inhibit, plasma protein levels of IL-1α, IL-6, IL-8, MCP-1, MIP-1β, MMP-3, and TNF-α. After 40 weeks of treatment with apremilast, there was a decrease in plasma protein levels of IL-17 and IL- 23, and an increase in IL-10. In clinical studies in patients with psoriasis,

apremilast decreased lesional skin epidermal thickness, inflammatory cell infiltration, and expression of pro-inflammatory genes, including those for inducible nitric oxide synthase (iNOS), IL-12/IL-23p40, IL-17A, IL-22 and IL-8. In clinical studies in patients with Behçet Disease treated with apremilast, there was a significant positive association between the change in plasma TNF-alpha and clinical efficacy as measured by the number of oral ulcers. Apremilast administered at doses of up to 50 mg twice daily did not prolong the QT interval in healthy subjects

IV.4 Clinical Efficacy

The efficacy of apremilast in the proposed indications is established in clinical use. No new clinical efficacy studies are provided and none are required.

IV.5 Clinical Safety

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Apremilast film coated tablets.

Part II. Safety specification
The proposed Summary of safety concerns (RMP Part II: Module SVIII) is included below.
It is aligned with the safety specification of the reference product and is (thus) considered appropriate.

Summary of safety concerns	
Important identified risks	• Serious events of hypersensitivity • Suicidality • Serious events of depression
Important potential risks	• Vasculitis • Malignancies • Serious events of anxiety and nervousness • Serious infections including opportunistic infections and transmission of infections through live vaccines • Major adverse cardiac event (MACE) and tachyarrhythmia • Prenatal embryo-fetal loss and delayed fetal development (reduced ossification and fetal weight) in pregnant women exposed to apremilast
Missing information	• Long term safety

Part III. Pharmacovigilance Plan
Routine pharmacovigilance is suggested, and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:
Specific adverse reaction follow-up questionnaires for following risks are presented in
Annex 4 of the RMP and are in line with the reference medicinal product, which is endorsed.

Part V. Risk minimisation measures
The Applicant concludes that the safety information in the proposed product information is aligned to the reference medicinal product; no additional risk minimisation activities are proposed, which is endorsed.

Periodic safety update reports (PSURs) shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicine's web-portal.

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 submitted the results of a suitable bioequivalence study, which has demonstrated the similarity of the Apremilast 30 mg film-coated tablets of axunio with the pharmacokinetic profile of the reference product Otezla 30 mg film-coated tablets of Amgen Europe B.V. Minervum 7061, 4817 ZK Breda, Netherlands in accordance with the relevant guidance. A justification for waiver of a study with the 10 mg and 20 mg strength has been provided. No additional tests are required for this application.

V. OVERALL CONCLUSIONS

Apremilast axunio 30 mg film-coated tablets is a generic form of Otezla 10 mg, 20 mg & 30 mg film-coated tablets. Otezla 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 Apremilast axunio 30 mg film-coated tablets demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

03/09/2030