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Public Assessment Report

Scientific discussion

Apremilast Noucor 30 mg film-coated tablets (Apremilast)

ES/H/0920/001/DC

Date: 26 February 2026

This module reflects the scientific discussion for the approval of Apremilast Noucor 30 mg film-coated tablets. The procedure was finalised at 28th/10/2024. For information on changes after this date, please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Apremilast Noucor 30 mg film-coated tablets, from Noucor Health S.A.

The product is indicated for*:*

- Psoriatic arthritis/ Apremilast, 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/ 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/ treatment of adult patients with oral ulcers associated with Behçet's disease (BD) who are candidates for systemic therapy

A comprehensive description of the indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10.1 of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

The finished product is presented as film-coated tablets containing 30 mg of Apremilast as active substance. The maximum daily dose is 60 mg.
The product is available in PVC/ACLAR/PVC-Aluminium blister as described in section 6.5 of the SmPC.

II.2 2.2Drug Substance

The quality of the drug substance is supported by ASMFs.

General Information

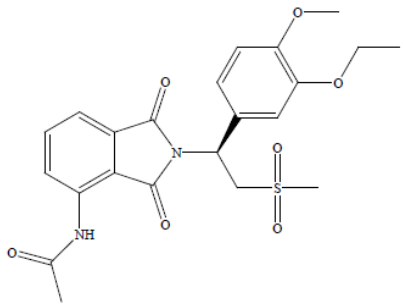
Nomenclature:

INN: Apremilast

Chemical name: N-{2-[(1S)-1-(3-Ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl}acetamide

CAS-No: 608141-41-9

Structure:



Molecular Formula
$C_{22}H_{24}N_2O_7S$

Relative Molecular Mass
Mr: 460.5 g/mol

General Properties:

Appearance

White to pale yellow powder.

Solubility

Apremilast is freely soluble in acetonitrile, DMF and methylene chloride; soluble in acetone and THF; sparingly soluble in ethyl acetate; very slightly soluble in methanol, ethanol and toluene; and practically insoluble in water, methyl tert-buthyl ether, NaOH 1N and HCl 1N solution.

pKa

pKa = 12.58

Melting point

156.7ºC

Polymorphism

Apremilast exhibits polymorphism.

Isomerism

Apremilast has an asymmetric carbon atom which gives rise to two enantiomers (R-Apremilast and S-Apremilast). The active isomer is the S-Apremilast, therefore the enantiomer R-Apremilast is considered an impurity.

Hygroscopicity

Apremilast is a non-hygroscopic product.

Manufacture, process controls and characterisation

The description of the manufacturing process is properly detailed. The specifications of the materials used in the synthesis are sufficient and adequate. The profile of impurities, including residual solvents, of these materials which can influence the quality of the active substance are well defined and controlled.

The acceptance criteria for the critical stages and the information on the quality and control of intermediates are adequate.

Specification, analytical procedures, batch analysis

Active substance specifications are considered appropriate and limits justified. Analytical methods are correctly described and validation carried out according to ICH. Batch results support consistent production.

Container closure system

The choice of the container closure system is properly justified. Compliance with the relevant requirements and/or regulations is confirmed.

Stability

Stability studies have been performed in accordance with current guidelines. Protocol, controlled parameters and test methods are considered adequate. The packaging material is similar to that proposed for storage. Proposed re-test period and storage conditions are justified.

II.3 Medicinal Product

Description of the product

Apremilast 30 mg film-coated tablets are beige, 9.5 mm diameter, biconvex round film coated tablets.
The active substance is apremilast, each film-coated tablet contains 30 mg of apremilast.
The other ingredients in the tablet core are microcrystalline cellulose, croscarmellose sodium, colloidal anhydrous silica and magnesium stearate.
The film-coating contains poly(vinyl alcohol), titanium dioxide (E171), macrogol, talc, iron oxide red (E172), iron oxide yellow (E172) and ferrosoferric oxide/black iron oxide (E172).
Apremilast 30 mg film-coated tablets are packed in PVC/ACLAR/PVC-Aluminium blister.

Pharmaceutical Development

The development of the product has been described, the choice of excipients is justified and their functions explained.
The physicochemical characteristics of the active substance that may affect the pharmaceutical form are identified and their control strategy is justified.
The choice of dissolution method is considered appropriate. The information presented supports the proposed quality control dissolution method.

Manufacture of the product

The manufacturing process is fully described and in-process controls are appropriate considering the nature of the product and the manufacturing process. The industrial batch size is well-defined.

The process validation scheme is provided.

Excipients

Excipients used are well known and of appropriate quality.

None of the excipients is of animal origin.

Product specification, analytical procedures, batch analysis

The finished product specifications are adequate to control the finished product. Provided description and validation data for the analytical methods are adequate. Batch analysis data have been submitted and the results show that the finished product meets the proposed release specification.

Container closure system

The finished product is packaged in PVC/ACLAR/PVC-Aluminium blister. The choice of the container closure system is justified considering the nature of the finished product. Compliance with the relevant requirements and/or regulations is confirmed.

Stability

Stability studies have been performed in accordance with current guidelines. The proposed protocol is considered adequate. The packaging material is the same as that intended for marketing. Proposed shelf-life and storage conditions are properly established.

Shelf-life: 2 years.

Storage conditions: This medicinal product does not require any special storage conditions.

III. NON-CLINICAL ASPECTS

III.1 Critical evaluation of the Non-Clinical Overview

Pharmacodynamic, pharmacokinetic and toxicological properties of apremilast are well known. As apremilast is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

III.2 Environmental Risk Assessment (ERA)

Since Apremilast Noucor 30 mg film-coated tablets is a generic product, it will not lead to an increased exposure to the environment. Therefore, additional ERA studies are not deemed necessary.

IV. CLINICAL ASPECTS

IV.1 Introduction

Apremilast is a well-known active substance with established efficacy and safety. A clinical overview has been provided, which is based on scientific literature. The clinical overview justifies that there no need to generate additional clinical data.

For this generic application of an immediate release formulation, the MAH has submitted one bioequivalence study with the 30 mg strength according to the Guideline on the investigation of bioequivalence, which is discussed below.

IV.2 Pharmacokinetics

<u>Biowaiver</u>
NA

Bioequivalence studies

Study code
APR-0522-54

GCP compliance
The study was conducted in accordance with Good Clinical Practice (GCP) standards. Monitoring reports and certificates of audits carried out by the Quality Assurance Unit are presented. The sites have been previously inspected by EU regulatory authorities.

Clinical and analytical facilities
Clinical and analytical sites: International Pharmaceutical Research Centre (IPRC). Sport City Circle, Amman, Jordan. Sport City Circle, Amman, Jordan.

Design.
A randomised, single-dose, two-treatment, two-period, two sequence, crossover bioequivalence study was carried out under fasted conditions in 38 healthy male subjects, aged 18 – 48 years. Each subject received a single dose (30 mg tablet) of one of the two active substance formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least ten hours. There were two dosing periods, separated by a washout period of 7 days.

Analytical and statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples.
The 90% confidence interval (90% CI) of the ratio of the test formulation to the reference formulation for the log-transformed values of Cmax and AUC was calculated using an ANOVA model. This model included the covariates sequence, period, formulation and subject nested to sequence. Bioequivalence was defined when the 90% CI of the ratios (test/reference) for Cmax and AUC was in the range 80.00 -125.00%.
The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
38 subjects, were included in the study and completed the study and 38 were used in the statistical analysis according to the protocol.
The inclusion and exclusion criteria are considered acceptable for a bioequivalence study.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment	**AUC_{0-t}** ng/ml/h	**$AUC_{0-\infty}$** ng/ml/h	**C_{max}** ng/ml	**t_{max}** h
Test [N=38]	2701.2± 893.02	2815.5± 940.66	292.231± 78.23	2.67 (1.00- 5.00)
Reference [N=38]	2694.8± 1064.35	2819.2± 1109.88	290.293± 84.01	2.33 (0.67- 5.00)
***Ratio (90% CI)**	102.02 (**97.36-106.90**)	NR	100.61 (**94.04-107.64**)	

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.
AUC_{0-72h} can be reported instead of AUC_{0-t}, in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.
$AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}

C_{max}	Maximum plasma concentration
t_{max}	Time until Cmax is reached

**ln-transformed values*

Conclusion on bioequivalence studies:
Based on the submitted bioequivalence study Apremilast Noucori 30 mg film coated tablets is considered bioequivalent with Otezla 30 mg film-coated tablets (

IV.3 Pharmacodynamics

NA

IV.4 Clinical efficacy

NA

IV.5 Clinical safety

NA

IV.6 Risk Management Plan

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 Noucor 30 mg film-coated tablets (apremilast).

- Summary table of safety concerns as approved in RMP

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. − MACE and tachyarrhythmia − Prenatal embryo-fetal loss and delayed fetal development (reduced ossification and fetal weight} in pregnant women exposed to apremilast
Important missing information	− Long-term safety

There are neither proposed additional pharmacovigilance activities nor proposed additional risk minimisation measures planned for Apremilast Noucor 30 mg film-coated tablets (apremilast).

IV.7 Discussion on the clinical aspects

For generic applications please refer to section IV.2.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Otezla authorised by centralised application and the nationally authorised product Memantine 10 mg film-coated tablets. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product Apremilast Noucor is found adequate. There are no objections to the approval of Apremilast Noucor 30 mg film coated tablets from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.