LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Apremilast Teva
(apremilast)

SE/H/2304/01-02/DC

This module reflects the scientific discussion for the approval of Apremilast Teva. The procedure was finalised on 2024-05-29. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Apremilast Teva, 10 mg + 20 mg + 30 mg, 30 mg, Film-coated tablet.

The active substance is apremilast. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Apremilast Teva, 10 mg + 20 mg + 30 mg, and 30 mg, respectively, film-coated tablet, is a generic application submitted according to Article 10(1) of Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and AT, BE, ~~BG~~, CZ, DE, DK, EL, ES, FR, ~~HR~~, IT, NL, PL and SK as concerned member states (CMS) for strength 01; and AT, BE, ~~BG~~, CZ, DE, DK, EL, ES, FI, FR, ~~HR~~, IT, ~~LT~~, NL, PL and SK, for strength 02.
BG, HR and LT were withdrawn at day 160.

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Otezla, 30 mg, film-coated tablets, authorised in EU since 2015, with Amgen Europe BV as marketing authorisation holder.

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacology/Pharmacokinetics/Toxicology

Pharmacodynamic, pharmacokinetic and toxicological properties of apremilast are well known. As apremilast is a widely used, well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Apremilast Teva is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Apremilast Teva from a non-clinical point of view.

IV. CLINICAL ASPECTS

To support the marketing authorisation application the applicant has conducted one (1) bioequivalence study comparing Apremilast, 30 mg, film-coated tablet, with the reference product Otezla, 30 mg, film-coated tablets.

Pharmacokinetic properties of the active substance
Absorption: Apremilast has an oral bioavailability of approximately 73% %. Following an oral dose of apremilast maximal plasma concentrations occur at approximately 2.5 hours.

The pharmacokinetics of apremilast is not affected by food, and therefore there are no restrictions with respect to food in the SmPC of the originator.

Linearity: The pharmacokinetics of apremilast is linear within the dose range 10-100 mg.

Elimination: The terminal half-life is approximately 9 hours.

Study BE-2034-20 – 30 MG, FASTING
Methods
This was a single-dose, two-way crossover study conducted in 51 healthy volunteers, comparing Apremilast, 30 mg, film-coated tablet with Otezla, 30 mg, film-coated tablets under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 36 hours post-dose. Plasma concentrations of apremilast were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 2020-11-04 and 2020-12-01.

Results

The results from the pharmacokinetic and statistical analysis are presented in Table 1 below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for apremilast, n=51.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**3051.29 ± 975.31**	**344.04 ± 78.30**	**2.50 (0.67-5.00)**
Reference	**3170.81 ± 916.27**	**371.15 ± 86.61**	**3.00 (0.67-5.02)**
***Ratio (90% CI)**	**95.42 (92.13 - 98.82)**	**92.84 (89.47 - 96.33)**	**-**
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours C_{max} maximum plasma concentration t_{max} time for maximum plasma concentration			

**calculated based on ln-transformed data*

For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

A biowaiver was sought for the additional strengths of 10 mg and 20 mg.

Discussion and overall conclusion
The bioequivalence study and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr). The bioanalytical methods were adequately validated.

The results of study BE-2034-20 with 30 mg formulation CAN be extrapolated to the other strengths 10 mg and 20 mg, according to conditions in the Guideline on the investigation of Bioequivalence; CPMP/EWP/QWP/1401/98 Rev. 1, section 4.1.6.

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

Risk Management Plan
The Applicant 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 Teva.

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.
Of note, according to the agreed RMP of the reference product *non-conditioned* event-specific follow-up questionnaires are used (or have been used) for some of the important identified/potential risks. Also, a category 3 post-authorisation surveillance study (PASS) to evaluate the long-term safety of apremilast is still ongoing. However, no follow-up questionnaire or surveillance study is mentioned in the RMP submitted in the application for Apremilast Teva, which is considered acceptable for a generic application.

Part V. Risk minimisation measures
Routine risk minimisation is suggested, and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Part VI. Summary of the RMP
The proposed RMP for Apremilast Teva is adequately summarised by the Applicant.

Conclusion of the RMP assessment
The submitted Risk Management Plan, version 0.1, signed 15 Dec 2022, is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

Periodic Safety Update Report (PSUR)
Active substance is currently listed in the published EURD list

With regard to PSUR submission, the MAH should take the following into account:

- 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 medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

Common renewal date
The common renewal date will be 5 years after closure of the DCP.

V. USER CONSULTATION

The provided bridging report was assessed and accepted at day 120.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Apremilast Teva, is found adequate.
There are no objections to approval of Apremilast Teva 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.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Apremilast Teva, 10 mg + 20 mg + 30 mg, 30 mg, Film-coated tablet was positively finalised on 2024-05-29.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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