COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Tivlemaq 10 mg, 20 mg, 30 mg and Tivlemaq 30 mg film-coated tablets (apremilast)

NL/H/5722/001-002/DC

Date: 10 April 2025

This module reflects the scientific discussion for the approval of Tivlemaq 10 mg, 20 mg, 30 mg and Tivlemaq 30 mg, film-coated tablets. The procedure was finalised on 17 April 2024. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Tivlemaq 10 mg, 20 mg, 30 mg and Tivlemaq 30 mg, film-coated tablets, from Sandoz B.V.

The product is indicated for:

- Psoriatic arthritis

Tivlemaq 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 of the SmPC).

- Psoriasis

Tivlemaq is 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

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

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

As indicated in the section 'Posology and method of administration' of the SmPC, the recommended daily dose per day is taken in divided doses according to the initial dose titration schedule. Therefore, the medical product is presented in an initiation pack which includes the strengths 10 mg, 20 mg and 30 mg. Additionally, the 30 mg strength is presented in separate packaging for regular use after the initial titration.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this decentralised procedure, essential similarity is proven between the new product and the innovator product Otezla 10 mg, 20 mg and 30 mg film-coated tablets, Amgen Europe B.V., which has been registered in the EEA via a centralised procedure (EU/1/14/981, EMEA/H/C/3746) since 16 January 2015.

The concerned member states (CMS) involved in this procedure were Austria, Bulgaria, Croatia, Poland, Slovenia and Slovakia.

II. QUALITY ASPECTS

II.1 Introduction

Tivlemaq are film-coated tablets containing 10 mg, 20 mg or 30 mg apremilast as active substance. The film-coated tablets of the different strengths can be distinguished by their colour, size and debossing and are as follows:

Tivlemaq 10 mg is a light pink, oval, unscored film-coated tablet of approximately 8 mm length and 4 mm width, with 'AM' engraved on one side and '10' on the other side.

Tivlemaq 20 mg is a light brown, oval, unscored film-coated tablet approximately 10 mm length and 5 mm width, with 'AM' engraved on one side and '20' on the other side.

Tivlemaq 30 mg is a pink, oval, unscored film-coated tablet approximately 11 mm length and 6 mm width, with 'AM' engraved on one side and '30' on the other side.

The excipients are:
Tablet core- lactose monohydrate, microcrystalline cellulose (E460), croscarmellose sodium (E468) and magnesium stearate (E470b).

Film-coating- hypromellose 2910 (E464), lactose monohydrate, titanium dioxide (E171), macrogol 3350 (E1521) and iron red oxide (E172), iron oxide yellow (E172) (only for 20 mg and 30 mg strengths) and ferrosoferric oxide (E172) (only for 30 mg strength).

The tablet cores are dose proportional.

The film-coated tablets are packed in aluminium polyvinyl chloride (Alu-PVC) blisters or unit-dose blisters. The strengths 10 mg, 20 mg and 30 mg are included in an initiation pack. The strength 30 mg is also presented in separated packs.

II.2 Drug Substance

The active substance is apremilast, an established active substance which has not been described in any Pharmacopoeia. The active substance is a crystalline powder. It is practically insoluble soluble in water, slightly soluble in methanol and freely soluble in methylene chloride. The active substance is chiral, with two possible enantiomers and it shows polymorphism. For this product, polymorphic B form is consistently manufactured and sufficiently controlled.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent

Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

Apremilast is synthesised in six reaction steps followed by purification. The proposed starting materials and solvents are acceptable. The active substance, starting materials solvents and reagents used in the synthesis have been adequately characterised and adequate specifications are adopted to control their quality.

Quality control of drug substance

The active substance specification has been established in-house by the MAH and is considered adequate to control the quality. The specification is acceptable in view of the route of synthesis and the various European guidelines. As requested, the limits for enantiomeric purity, has been updated in line with the ASMF and the EMA guideline for the chemistry of active substances. Based on submitted data, the analytical method used and the new limits are found suitable, however a new concentration of a test solution will be used as committed by MAH (see section II.4). Batch analytical data demonstrating compliance with the specification have been provided for three batches.

Stability of drug substance

Stability data on the active substance have been provided for six production scale batches in accordance with applicable European guidelines. Based on the data submitted, a retest period could be granted of 4 years when stored under the stated conditions.

II.3 Medicinal Product

Pharmaceutical development

Tivlemaq is an immediate-release, film-coated tablet containing apremilast. The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. During development, optimisation tests were performed with different excipients and film-coating. The choice of excipients is justified and their functions explained. The choices of the packaging and manufacturing process are justified in relation to the innovator product. Overall, the pharmaceutical development of the product has been adequately performed. A bioequivalence (BE) study has been performed with the 30 mg product strength. The test batch used in the BE study was manufactured according to the finalised formulation and manufacturing process and at a representative scale. A biowaiver of strengths has been requested for the lower strengths 10 mg and 20 mg, see details in section IV.2. The development of the QC dissolution method is accepted, and the selected method is in line with the FDA method for this product. The discriminatory power of the method has been adequately demonstrated. The dissolution test limit has been adequately set in line with the dissolution profile of the bio batch.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three production scale batches of each strength.

Control of excipients
All excipients comply with the current version of the relevant Ph. Eur. monograph, except for the coating mixes for which in-house specifications are presented. For the excipients of the cores, adequately justified functionality related characteristics are included in the specifications. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, dimensions, identity, uniformity of dosage units (content uniformity), water content, dissolution, assay, related substances and microbial quality. Release and shelf-life limits are identical for all parameters except water content. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three production scale batches of each strength from the proposed production site(s) have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for three production scale batches of each strength stored at 25°C/ 60% RH (36 months), 30°/65% RH (12 months) and 40°C/75% RH (6 months). The stability was tested in accordance with applicable European guidelines. For all three strengths the impurity levels and assay results remain stable. Microbiological data complies to the limits throughout the shelf life. Dissolution results decrease; however, all batches comply to the specification limits according to the requirements of Ph. Eur. 2.9.3. Photostability studies were adequately performed and show that the product is not sensitive to light. On basis of the data submitted, a shelf life was granted of 3 years. No specific storage conditions needed to be included in the SmPC or on the label.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM for the excipient lactose monohydrate have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated. A certificate for magnesium stearate of vegetable origin has been submitted.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Tivlemaq has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made by the MAH:
- To use a new concentration of a test solution for the enantiomeric purity test.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Tivlemaq is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Otezla which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Apremilast is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The member states agreed that no further clinical studies are required, besides the bioequivalence study discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Tivlemaq 30 mg, film-coated tablets (Sandoz GmbH, Austria) was compared with the pharmacokinetic profile of the reference product Otezla 30 mg film-coated tablets (Amgen Europe B.V., the Netherlands). For the lowers strengths 10 mg and 20 mg, a biowaiver was requested.

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution study results and composition. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

Biowaiver

Apremilast has been classified as an BCS Class IV compound (low solubility/low permeability) PSD and hardness were chosen for the demonstration of discriminatory power. This is in line with the EMA Reflection paper on the dissolution specification for generic solid oral immediate release products). For apremilast there is a linear pharmacokinetic behaviour over

the therapeutic dose range. The following general requirements were met for the waiver for additional strength, according to the EMA Bioequivalence guideline:

a. the pharmaceutical products are manufactured by the same manufacturing process,
b. the qualitative composition of the different strengths is the same,
c. the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule),
d. appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

Comparative dissolution at pH 1.2, 4.5 and 6.8 was investigated according to the EMA Bioequivalence guideline. Comparative dissolution profiles between the different strengths and between the test and reference products used in the BE study at the 3 pH values have been provided, in all cases similarity has been demonstrated. The calculated f_2 similarity factor values were within criteria (>50%). An f_2 value between 50 and 100% suggests that the two dissolution profiles are similar. The biowaiver of strength for the 10 mg and 20 mg tablets is therefore considered acceptable.

Bioequivalence study

Design

A single-dose, open label, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 36 healthy male and female subjects, aged 19-55 years. Each subject received a single dose (30 mg) of one of the two apremilast formulations. The tablet was orally administered with 240±5 mL water after a 10-hour fasting period. The subjects fasted until at least 4 hours post-dose. Water was restricted from 1 hour prior to drug administration until 1 hour post-dose (except the water administered with the drug). There were two dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose (0 hours) and at 0.17, 0.33, 0.7, 1, 1.3, 1.7, 2, 2.3, 2.7, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 24 and 36 hours after administration of the products.

The design of the study is acceptable.

Apremilast may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of apremilast. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

A total of 34 of the 36 enrolled subjects completed both periods of the study and were eligible for pharmacokinetic analysis. Two subjects were withdrawn from the study, one due to a mild adverse event (vomiting) in period 1 and one due to personal reasons in period 2.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of apremilast, 30 mg, under fasted conditions.

Treatment N=34	**AUC_{0-t}** (ng.h/mL)	**$AUC_{0-\infty}$** (ng.h/mL)	**C_{max}** (ng/mL)	**t_{max}** (h)
Test	3590 ± 1318	3963 ± 1618	357 ± 85	3.00 (1.00 – 6.00)
Reference	3618 ± 1539	3969 ± 1892	389 ± 100	3.00 (0.67 – 6.00)
***Ratio (90% CI)**	1.01 (0.97 – 1.05)	---	0.92 (0.87– 0.97)	---

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to the last measurable plasma concentration / to t = 36 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Conclusion on bioequivalence study:

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Tivlemaq 30 mg is considered bioequivalent with Otezla 30 mg.

The results of the bioequivalence study with the 30 mg formulation can be extrapolated to the other strengths 10 mg and 20 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 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 Tivlemaq. At the time of approval, the most recent version of the RMP was version 1.1, signed 22 August 2023.

Table 2. Summary table of safety concerns as approved in RMP

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 expose to apremilast
Missing information	- Long-term safety

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Otezla. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC.

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Otezla 10 mg, 20 mg and 30 mg and the 30 mg film-coated tablets EU/1/14/981, EMEA/H/C/3746 for content and to Alendroninezuur/Cholecalciferol Sandoz 70 mg and 140 mg tablets, NL/H/3578/001/DC and NL/H/3587/001/DC for design and layout. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Tivlemaq 10 mg, 20 mg, 30 mg and Tivlemaq 30 mg, film-coated tablets, have a proven chemical-pharmaceutical quality and are generic forms of Otezla 10 mg, 20 mg and 30 mg film-coated tablets. Otezla is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

In the Board meeting 1050 of 4 April 2024, the following was discussed:
During this procedure Major Objections (MO's) were raised due to insufficient control of the content of a specific substance in the solvents used and due to the limits for the dissolution test for the final product. Both MO's constitute grounds for refusal when not resolved before the end of the procedure. To resolve the MO's, the MAH has added a routine control in the specification for the drug substance. Data has been submitted and the used analytical methods were described with sufficient details. The control of the substance is adequately performed. Furthermore, the limits for the dissolution test for the final product has been adjusted as requested. Boths MO's have been resolved before the end of the procedure and the application is found approvable.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Tivlemaq with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 17 April 2024.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/5722/ 001-2/P/001	Artikel 61(3): to correct a discrepancy in the outer labelling	Yes	28-10-2024	Approved	N.A.
NL/H/5722/ 001-2/ IA/001/G	Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product: - Secondary packaging site. Change to importer, batch release arrangements and quality control testing of the finished product: - Replacement or addition of a manufacturer responsible for importation and/or batch release. Including batch control/testing.	No Yes	17-3-2025	Approved	N.A.