EMA/471783/2024
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal assessment report

Apremilast Viatris

International non-proprietary name: apremilast

Procedure No. EMEA/H/C/006193/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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List of abbreviations

AE	Adverse Event
AUC	Area Under the plasma Concentration
$AUC_{0\text{-}inf}$	Area Under the plasma Concentration-time curve from time zero to infinity
$AUC_{0\text{-}t}$	Area Under the plasma Concentration-time curve from time zero to t hours
BE	Bioequivalence
BLQ	Below Limit of Quantification
C_{max}	maximum plasma Concentration
CHMP	Committee for Human Medicine Products
CoA	Certificate of Analysis
CP	Centralised procedure
CRF	Case Report Form
CRO	Certified Research Organisation
CV	Curriculum Vitae (1), Coefficient of Variation (2)
FDA	Food and Drug Agency
EMA	European Medicines Agency
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
IEC	Independent Ethics Committee
ISR	Incurred Sample Reanalysis
ISTD	Internal Standard
K_2EDTA	Dipotassium Ethylenediaminetetraacetic Acid
LC	Liquid Chromatography
LLOQ	Lower Limit of Quantification
LOQ	(1) Limit of Quantification, (2) List of Questions
LS	Least Squares
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MHRA	British National Competent Authority
MS	Mass Spectrometry
ng	Nanogram
QA	Quality Assurance
rpm	revolutions per minute
SOP	Standard Operating Procedure
SD	Standard Deviation
T/R	Test/Reference
T_{max}	Time for maximum concentration (* median, range)
$T_{1/2}$	terminal half-life
VR	Validation Report
WHO	World Health Organisation

1. CHMP recommendation

Based on the review of the data and the applicant's response to the CHMP on quality, and clinical, the generic application for Apremilast 10 mg, 20 mg and 30 mg film coated tablets in the treatment of psoriathic artritis, artritis and Behçet's disease, is not approvable, as there are two outstanding major objections (MOs), one on the bioequivalence and one on the quality of the active substance. Before approval, satisfactory answers should be also given to the "other concerns" as detailed in the List of Outstanding Issues. Failure to resolve may render the application not approvable.

1.1. Questions to be posed to additional experts

The CHMP has adopted a request for methodology working party (MWP) input on how the level of evidence should be assessed based on a pooled analysis of the 2 bioequivalence studies.

1.2. Proposal for inspection

None.

1.2.1. GMP inspection(s)

Not required.

1.2.2. GCP inspection(s)

Not required.

1.3. Similarity with authorised orphan medicinal products

N/A

1.4. Derogation(s) from market exclusivity

N/A

2. Executive summary

2.1. Problem statement

2.2. About the product

The product Apremilast Viatris 10 mg, 20 mg and 30 mg film-coated tablets was developed as a generic equivalent to the innovator's product Otezla 10 mg, 20 mg and 30 mg film-coated tablets. The reference product Otezla was authorised in the EU on 15.01.2015.

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 8 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.

The targeted indication for Apremilast Viatris 10 mg, 20 mg and 30 mg film-coated tablets states as follows:

- *"Psoriatic arthritis*: *Apremilast Viatris, 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.*
- *Psoriasis*: *Apremilast Viatris 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*: *Apremilast Viatris is indicated for the treatment of adult patients with oral ulcers associated with Behçet's disease (BD) who are candidates for systemic therapy."*

The proposed posology states as follows:

The recommended dose of apremilast is 30 mg taken orally twice daily, approximately 12 hours apart (morning and evening), with no food restrictions. An initial titration schedule is required as shown below in Table 1. No re-titration is required after initial titration.

Table 1 Dose titration schedule

Day 1	Day 2		Day 3		Day 4		Day 5		Day 6 & thereafter	
AM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
10 mg	10 mg	10 mg	10 mg	20 mg	20 mg	20 mg	20 mg	30 mg	30 mg	30 mg

If patients miss a dose, the next dose should be taken as soon as possible. If it is close to the time for their next dose, the missed dose should not be taken and the next dose should be taken at the regular time.

2.3. The development programme/compliance with CHMP guidance/scientific advice

N/A

2.4. General comments on compliance with GMP, GLP, GCP

No issues have been identified that specifically demand for an inspection.

At the time of submission valid GMP certificates for all proposed sites were available in EudraGMP base. Also, at the time of submission adequate QP declarations are provided.

2.5. Type of application and other comments on the submitted dossier

2.5.1. Legal basis

- Article 10(1) of Directive 2001/83/EC

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 8 years in the EEA:

- Product name, strength, pharmaceutical form: Otezla 10 mg, 20 mg and 30 mg film-coated tablets
- Marketing authorisation holder: Amgen Europe BV, Netherlands
- Date of authorisation: 15.01.2015.
- Marketing authorisation granted by: Union
- Marketing authorisation number: EU/1/14/981/001-003

Medicinal product authorised in the Union /Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Otezla 10 mg, 20 mg and 30 mg film-coated tablets
- Marketing authorisation holder: Amgen Europe BV, Netherlands
- Date of authorisation: 15.01.2015.
- Marketing authorisation granted by: Union
- Marketing authorisation number: EU/1/14/981/001-003

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Otezla 30 mg film-coated tablets
- Marketing authorisation holder: Amgen Europe BV, Netherlands
- Date of authorisation: 15.01.2015.
- Marketing authorisation granted by: Union
- Marketing authorisation number: EU/1/14/981/001-003
- Bioavailability study number: C23132

2.5.2. Orphan designation

Not Applicable.

2.5.3. Similarity with orphan medicinal products

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

2.5.4. Derogation(s) from orphan market exclusivity

N/A

2.5.5. Information on paediatric requirements

Not applicable.

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

The finished product is presented as film-coated tablets containing 30 mg, 20 mg and 10 mg of apremilast as active substance.

Silicified microcrystalline cellulose (contains cellulose, microcrystalline and silica, colloidal anhydrous), croscarmellose sodium and magnesium stearate are used for tablet core. Polyvinyl alcohol, titanium dioxide (E171), macrogol /PEG 3350, talc, iron oxide red (E172), iron oxide yellow (E172) and iron oxide black (E172) are used for film coating.

The proposed dosing regimen of apremilast is 30 mg film-coated tablets with an initial titration phase (an initial titration schedule is required as shown in the proposed SmPC, section 4.2). Hence, a treatment is started with a dose of 10 mg on day 1 and gradually increased over a week to the recommended dose of 30 mg twice a day.

The product is available in PVC/Aluminium blister packs and perforated unit dose blisters, as well as in white opaque High Density Polyethylene (HDPE) bottles and a white opaque polypropylene (PP) fine ribbed continuous threaded closure with induction sealing liner wad in packs.

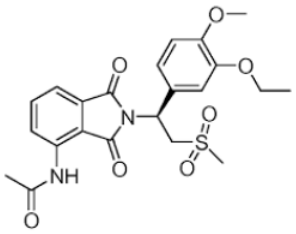
At the moment, the chemical-pharmaceutical documentation in relation to Apremilast Viatris is not of sufficient quality in view of the present European regulatory requirements.

3.1.2. Active substance

The active substance apremilast is not described in the current Ph. Eur.

3.1.2.1. General Information

The active substance apremilast (INN) belongs to therapeutic category of immunosuppressants, selective immunosuppressants (ATC code: L04AA32). Chemical name is: N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl] acetamide and corresponds to the molecular formula $C_{22}H_{24}N_2O_7S$. It has a relative molecular mass of 460.50 g/mol and the following structure:



The active substance (AS) is a white to pale yellow powder. Exhibits low solubility and low permeability (BCS Class IV) and solubility is pH-dependent (increases at high pH). It is slightly hygroscopic in nature, which is supported by data.

The active substance apremilast contains one chiral centre and hence exists in 2 isomeric forms i.e. (S)-isomer and (R)-isomer. Of the 2 isomers, (S)-isomer is the desired and the undesired (R)-isomer is controlled in the active substance specification as impurity.

Apremilast exhibits polymorphism and information on the different polymorphic forms which exist are presented. It is demonstrated that the manufacturer consistently produce the same, thermodynamically most stable crystalline form. The identification test of the polymorphic form by XRPD is included in the active substance specification. Stability of polymorph form is confirmed, supported by stability data presented in section S.7.3. Moreover, it is confirmed that polymorphic form is preserved after micronisation as well. However, regarding identification of claimed polymorphic Form-B further discussion/justification is requested.

From different sections of presented ASMF, it can be concluded that the active substance manufacturer provides the active substance as per the particle size requirement of finished product manufacturer.

3.1.2.2. Manufacture, process controls and characterisation

The proposed route of synthesis is considered appropriate and in general the manufacturing process descriptions are provided in sufficient detail. The manufacturing process of apremilast involves four steps. Information regarding batch sizes are adequately included in the AP-ASMF. Three starting materials are proposed and they are acceptable, since adequate justification of starting materials selection (in line with ICH Q11) is provided. Since active substance can be micronised upon customer requirement, short description of micronisation process as well as batch size of micronised active substance is provided.

No alternative steps and recovered solvents have been used in the manufacturing process of the AS. Reprocess procedures for steps 2, 3 and 4 are mentioned in the ASMF. From the presented data in the Restricted part, it can be concluded that the steps applied during reprocessing are the same as those that are part of the established manufacturing process and does not involve new solvents and/or materials.

Detailed information on the manufacturing of the active substance has been provided in the Restricted part of the ASMF. In-process controls have been adequately described. Critical process parameters and steps have been identified and acceptable.

The chemical structure of apremilast has been confirmed by various techniques like IR, UV, MS, 1H NMR, 13C NMR, elemental analysis and XRD with representative spectra included in the documentation.

A summary of the impurities which may be present in apremilast is provided in the ASMF. The impurities are classified as potential impurities from the raw materials, potential impurities from the manufacturing process and degradation of the drug substance.
Identified organic impurities have been listed with structures, names, origin as well as brief information on their control strategy has been provided. An assessment on the potential progression into the final active substance of impurities originating from starting materials and raw materials is appropriately presented.

All organic solvents used in the manufacturing process are routinely controlled in the active substance. The limits for residual solvents and impurities are in accordance with the respective ICH guidelines.

Initially, it was not possible to make a conclusion on presence of genotoxic impurities in active substance, since only the starting materials were verified for genotoxicity structural alerts and the sole method used was DEREK (QSAR) predictions. Hence, additional discussion has been requested. The applicant evaluated the possible presence of genotoxic impurities in apremilast, according to ICH guideline M7 using two complementary (Q)SAR methodologies. For all impurities adequate control has been proposed, expect for one impurity which is controlled in the active substance specification, which is not acceptable. This question is raised as MO.

For elemental impurities risk assessment according to ICH Q3D provided. No risks were identified. Screening of elemental impurities by validated ICP-MS was performed. Further controls in the AS are deemed unnecessary.

The active substance manufacturer has provided adequate documentation and discussion regarding of the outcome of risk assessment on nitrosamines. It can be confirmed that there is no risk relating to nitrosamine impurities to be carried over by AS in the finished product.

Apremilast is packed in clear LDPE bag, placed inside an outer black PE bag, further put in aluminium foil and placed into HM-HDPE container. Between two polyethylene bags a desiccant silica gel is inserted. The primary packaging material complies with EC 10/2011 as amended.

3.1.2.3. Specification (s)

Since no monograph exists in European Pharmacopoeia for apremilast, the active substance is controlled according to the in-house requirements. All relevant parameters have been specified (description, solubility, identification by IR and by HPLC, X-ray diffraction, loss on drying, sulphated ash, apremilast R-isomer by HPLC, assay, organic impurities, residual solvents, microbial quality and particle size). The test parameters included in the specification are generally in line with ICH Q6A.

All analytical methods used have been adequately described or a reference is made to Ph. Eur. The reference of each in-house analytical method is included in the specification. In general, the in-house methods are adequately validated. It is confirmed that the HPLC method for related substances is stability indicating (results of mass balance are enclosed).

Batch analysis data for adequate number of commercial batches of AS are provided. All batches comply with the proposed specification, and demonstrate the consistent quality of material.

Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

3.1.2.4. Stability

Stability data of batches conducted at accelerated (40°±2°C/75%±5%RH) and long-term conditions (25±2°C/60±% RH), stored in the intended commercial package are available. Overall 10 batches of AS have been put on stability testing. For all presented batches, accelerated studies have been completed.

All results remained within specifications at all testing time-points at both conditions. No obvious trends are observed for any of the tested parameters. The substance appears stable at long term and accelerated conditions. Moreover, there is no differences between the results enclosed. Polymorphic form was controlled within long term and accelerated stability study and found stable.

Based on stability data presented, the proposed re-test period could be accepted at the moment.

Active substance related to additional data provided by Applicant only

The finished product manufacturer has provided data on sections S.4 and S.5.

Since there is no compendial active substance monograph, the specification of apremilast is based on the in-house requirements.
Finished product manufacturer's specification for apremilast is identical as the active substance manufacturer's specification, except for particle size. Although the applicant states that non-micronised apremilast is used for finished product, considering low solubility of AS, the finished product manufacturer has established limits for particle size in three points. The PSD specification is in line with the distribution of the particle size of the AS batch that have been incorporated in the finished product batch that is used for the bio-equivalence (BE) study.
The validated analytical procedures used by the finished product manufacturer to test apremilast active substance are the same as those being followed by active substance manufacturer. Reference is given to the AP of the ASMF sections 3.2.S.4.2 and 3.2.S.4.3. In addition, the test method followed at the finished product manufacturing site has the following test parameters. i.e., particle size and microbiological test and adequate validation reports for these two methods are enclosed.

Batch analysis data on three AS batches (including AS batch utilised for manufacturing of BE batch) tested by the finished product manufacturer according to the proposed specification has been presented. The results are within the proposed specification.

Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

3.1.3. Finished Medicinal Product

3.1.3.1. Description of the product and Pharmaceutical Development

The finished product (FP) is an immediate release dosage form formulated as a film-coated tablet in 10 mg, 20 mg and 30 mg strength.

Apremilast 10 mg film-coated tablets	:	Pink color, round shaped, biconvex bevel-edged film coated tablets debossed **10** on one side and **V** on other side. Should be free from physical defects. **Diameter:** Approximately 6.8 mm
Apremilast 20 mg film-coated tablets		Brown color, round shaped, biconvex bevel-edged film coated tablets debossed **20** on one side and **V** on other side. Should be free from physical defects. **Diameter:** Approximately 8.3 mm
Apremilast 30 mg film-coated tablets	:	Beige color, round shaped, biconvex bevel-edge film coated tablets debossed **30** on one side and **V** on other side. Should be free from physical defects. **Diameter:** Approximately 9.4 mm

The composition details for film coating materials were provided.

All excipients are well known pharmaceutical ingredients. There are no novel excipients used in the finished product formulation. For most of the ingredients a reference is made to the Ph. Eur. or USP-NF, except for ready to use film coating dry mixture which is controlled according to the manufacturer's in-house. All the components of the coating are of Ph. Eur. quality or comply to the EU regulation 231/2012 (iron oxide red (E172), iron oxide black (E172) and iron oxide yellow (E172)). The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The qualitative and quantitative composition is well defined, and the final product is packaged into PVC/Al-Aluminium blisters (classical and unit-dose blister) or white HDPE bottles with white PP closure.

Pharmaceutical development

The finished product has been developed to be a generic equivalent to the reference medicinal product Otezla (apremilast) 10 mg, 20 mg and 30 mg film-coated tablets. Consequently, the objective was to prepare a film-coated tablet being essentially similar to the reference medicinal product. Apremilast Viatris 10 mg, 20 mg and 30 mg film coated tablets are essentially similar and contain the same active ingredient i.e. apremilast in a quantitative and qualitative terms. The excipients of FP are not fully comparable with the excipients of the reference product Otezla 10 mg, 20 mg and 30 mg strength, and the differences were explained.

Critical process parameters have been identified through systematic evaluation using risk assessment methodologies. Quality target product profile (QTPP) and critical quality attributes (CQAs) are used for finished product development. A summary of the knowledge gained throughout development experiments to production scale associated with processing parameters and their impact on critical quality attributes of film-coated tablets is provided. The process compensates for the variability in the material attributes. A control strategy of the material attributes and process parameters are proposed which includes in-process controls and finished product specifications.
As per the QTPP the final formulation, pharmaceutical form and manufacturing process were selected. No overages are used in the finished product.

No polymorphic change has been detected during finished product manufacturing and stability testing. Polymorphic identification test by PXRD is included in finished product manufacturer`s AS specification. It is acceptable that crystalline form is not controlled routinely during finished product manufacturing.

Apremilast has one centre of chirality and the R-isomer is controlled (by chiral HPLC method) in the finished product manufacturer`s active substance specification. Stability data for three batches of active substance are enclosed and indicates that apremilast R-isomer does not increase during stability (after 60 months at 40°C/75% RH & 25°C/60% RH, results remains as initial).

Comparison of impurity profiles of reference and test product has been presented. The presented result are comparable.

Apremilast exhibits low solubility (BCS Class IV). This is taken into account in the evaluation of suitability of the *in vitro* dissolution method and of the comparative dissolution profiles submitted for investigation of similarity.

Selection of dissolution parameters has been adequately explained. Discriminatory power of the method has been demonstrated.
Comparative dissolution studies have been performed between the test and the reference bio-batches according to QC method, as well as in two other media. The applicant has stated that since the test product has been proved to be bio-equivalent to the reference product under fasting conditions, therefore, it can be concluded that the difference in drug release profiles does not have any impact on

the *in vivo* performance of the test product. Adequate data for biowaiver have been also provided and reference is made to the clinical assessment report.
From the presented data there are no differences in the manufacturing processes of the commercial product and clinical trial material.

A detailed information has been provided on the development of the manufacturing method. Each stage of the manufacturing process has been evaluated following a process development risk assessment.

The selected container closer systems are common for this dosage form. The container closure system is suitable for use based on development studies.

3.1.3.2. Manufacture of the product and process controls

Apremilast film-coated tablets manufacturing process consists of following main steps: quantity verification of raw materials, sifting, blending, compression, film-coating and packaging. The process is considered to be a standard manufacturing process.

The overview of production process is provided, accompanied by a flow chart. The description of manufacturing process is in line with manufacturing process development provided under section P.2. Generally the provided data are considered sufficient for manufacturing procedures of conventional solid oral dosage formulation.

The information provided on the method of manufacture and the controls applied is generally acceptable. Enclosed narrative description is found to be acceptable.
Validation batches are also included in the formal stability studies. Enclosed validation data are found to be satisfactory.

The expiration period of a batch is calculated in accordance with the EU guideline Note for Guidance on Start of Shelf-Life of the Finished Dosage Form (CPMP/QWP/072/96).

3.1.3.3. Product specification (s)

The specifications for batch release and shelf-life for 10 mg, 20 mg and 30 mg is proposed. The specifications have been identified by a version and date of approval / effective date.

The release and shelf-life specifications include the same testing parameters such as Description, Dimension, Identification, Dissolution, Uniformity of dosage units, Related substances, Assay, Microbial test and Colour Identification tests. In both specifications the proposed acceptance criteria are the same for both strengths, except for appearance and dimension of tablet.
Hardness, average weight, friability and disintegration are tested as IPC during compression stage, this is considered sufficient.
Limits for uniformity of dosage units (by content uniformity) and microbiological quality are in line with the relevant Ph. Eur. monographs. The proposed limits for apremilast assay throughout the shelf life of the product are acceptable without further justification. Limits for all specified impurities are acceptable as well as proposed limit for any unknown impurity, since are in line with ICH Q3B and maximal daily dose of apremilast. In addition, limits for total impurities are acceptable as well as limit for water.

For proposed dissolution limit is requested to be in line with results for bio-batch, in accordance with the reflection paper. The applicant enclosed discussion for suggesting different limit than requested. Hence, question of dissolution limit is still unresolved.

The analytical procedures have been described in sufficient details and are adequate to control the finished product on a routine basis. Appropriate validations of proposed in-house methods in line with ICH requirements are enclosed.

Batch analysis data of three scale batches of each dosage strengths have been presented. All batches are showing compliance to the current specifications and batch-to-batch consistency is confirmed.

Risk assessment for elemental impurities is performed according to ICH Q3D Option 2b, based on the maximum daily intake of the drug and its excipients. Batch analysis data on one batch of each dosage strength is enclosed, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls.

Risk assessment for the finished product was provided considering possibility of nitrosamine impurities from active substance, excipients, packaging material, manufacturing process. The risk evaluation on nitrosamines for the finished product was conducted according to EMA Questions and answers EMA/409815/2020, ICH M7 and ICH Q9. The applicant concluded that no risk of nitrosamines presence in the concerned medicinal product was identified. The risk evaluation concerning the presence of nitrosamine impurities is considered acceptable for AS and bulk product. Relevant data is enclosed for primary packaging also. Therefore, no additional control measures are deemed necessary.

Satisfactory information regarding the reference standards used for assay and impurities testing has been presented. However adequate data regarding impurities standards utilised for validations of HPLC methods for assay and related substances, is missing and should be provided.

The selected container closer systems (HDPE bottle and blister pack PVC/Al) are common for this dosage form and blister packaging. Specifications, method of analysis and CoA's of all primary packaging materials as well as declarations of compliance, when relevant, with the EU Directive 10/2011 and amendments are provided. The materials complies with Ph. Eur. and EC requirements. Additionally, test for dimensions are included in HDPE container specification and drawings of the container closure systems presented.

Data regarding the bulk packaging have been provided and is acceptable.

3.1.3.4. Stability of the product

Stability study has been performed on three validation batches of each dosage strength. The samples were packed in the proposed market packaging, in accordance with current ICH/CHMP guidelines. Batches are tested according to the proposed specification provided in section P.5.1, and according to analytical procedures described in section P.5.2.

For primary packaging, PVC /Al blister and HDPE bottles (with 56 tablets and with 168 tablets of 30 mg strengths), results of stability study are provided up to 12 months for all tested batches at 25°C/60% RH. Stability is on-going for all batches. At 40°C/75% RH up to 6 months for all batches of all dosage strengths are enclosed (accelerated stability is finished).

All results are within proposed limits. Proposed shelf-life of 24 months for product packed in HDPE bottles and PVC/Al blister is acceptable (in line with ICH Q1E). According to enclosed stability results, this finished product does not require any special storage conditions. The unpackaged finished product is not sensitive to light.

The proposed holding time for the bulk film coated tablet is acceptable.

In-use stability

Stability after opening has been investigated. The in use stability is still on going, No in-use shelf-life has been applied in PI texts and this is supported by the currently available data from in-use and open-pot studies for the applied formulation of solid oral dosage form. Enclosed data for in-use stability testing is acceptable.

3.1.3.5. Adventitious agents

No excipients derived from animal or human origin have been used

3.1.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

Following the conducted in-silico (Q)SAR mutagenicity assessment and new data provided, potential mutagenicity has been observed for one impurity. A Major Objection is raised on the quality of the active substance.

Since no monograph exists in European Pharmacopoeia for apremilast, the active substance is controlled according to the in-house requirements. All relevant parameters have been specified. Overall, several other concerns have been raised in connection with identified issues during review of the data.

The description and composition of the finished product are in general satisfactorily described.

Formulation development was based on the composition of the reference product Otezla 10 mg, 20 mg and 30 mg film-coated tablet.

No major objection is raised during assessment of finished product documentation. Several other concerns about the different section of the documentation need to be clarified. The detailed information is given in the quality part of the assessment report.

3.1.5. Conclusions on the chemical, pharmaceutical and biological aspects

Apremilast Viatris 10 mg, 20 mg and 30 mg film-coated tablets cannot be recommended for approval, before satisfactory responses to the MO and other concerns, as outlined in the List of Questions, are provided.

3.1.6. Recommendations for future quality development

Not applicable.

3.2. Non-clinical aspects

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.

It is considered that the non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

3.2.1. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment studies were submitted. This was justified by the applicant as the introduction of Apremilast Viatris manufactured by Viatris Limited is considered unlikely to result in any significant increase in the combined sales volumes for all apremilast containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar.

3.2.2. Discussion on non-clinical aspects

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate. An assessment of the impurities and degradants present in the active substance and

product, along with what is known of their potential pharmacologic and toxicologic effects, is included. Module 2.4 has been adequately dated.

ERA

Increase of apremilast consumption is seen in almost all countries in EU, especially seeing that the consumption for the two quarters of 2023 is practically equal to or higher than consumption for the entire year of 2022. However, in all individual EU member states the $PEC_{SURFACEWATER}$ refined based on consumption data was below 0.01 µg/L. In most cases, even if $PEC_{SURFCEWATER}$ for 2023 would be doubled, the expected concentration would stay below the action limit. Since in the past apremilast was considered unlikely to represent a risk to the environment based on even higher PEC than it was calculated here, it is considered that marketing authorization of the proposed product will not lead to any increased environmental risk.

3.2.3. Conclusion on non-clinical aspects

Non-clinical part of the proposed SmPC is identical to the reference product.

Overview based on literature review is appropriate and has adequately been dated, so there are no further remarks. Justification for not providing ERA is acceptable.

3.3. Clinical aspects

A clinical expert has written the clinical overview. The report, written in 2023, refers to 51 publications dating up to year 2023. The Clinical Overview on the clinical pharmacology, efficacy and safety of apremilast is adequate.

The clinical parts of the proposed SmPC are in line to the SmPC of the originator product.

The proposed pack sizes correspond to the originator's pack sizes range and are considered acceptable.

3.3.1. Exemption

To support the application, the applicant has submitted two identically designed bioequivalence studies with 30 mg strength, of which one (study C22175) failed and another (study C23132) succeeded to prove bioequivalence, as well as pooled analysis of both studies to support the BE claim.

The biowaiver is proposed for Apremilast Viatris 10 mg and 20 mg film-coated tablets. The requirements for biowaiver according to the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1/Corr** are considered fulfilled (same manufacturing process, same qualitative composition and dose proportionality, linearity of apremilast pharmacokinetics, as well as appropriate *in vitro* dissolution data).

Even though the biowaier is acceptable, bioequivalence still needs to be demonstrated for the higher 30 mg strength.

3.3.2. Clinical pharmacology

3.3.2.1. Pharmacokinetics

Study C23132

Methods

- **Study design**

This was an open label, balanced, randomized, two-treatment, two-period, two sequence, single-dose, cross-over, oral bioequivalence study of Apremilast 30 mg film-coated tablets compared with Otezla (Apremilast) Amgen Europe B.V. in thirty-eight (38) subjects under fasting conditions.

Study plan and subjects' randomization:

This was a single dose oral bioequivalence study under fasting conditions. This study was an open labelled study and hence the subjects and the investigators were not blinded towards the identity of the test and reference products. In each study period, a single oral dose of either test product (T) or reference product (R) was administered orally. The order of receiving Test product (T) or Reference product (R) for each of 38 subjects during each period of the study was determined according to a randomization schedule, generated by using PROC PLAN procedure. As per protocol, a wash-out period of at least 07 days was considered adequate to prevent carry-over in next period, considering the same, a wash-out period of 07 days for Group-1 period-1 to period-2.

Drug intake procedures:

All subjects had fasted overnight for 10.00 hours prior to dosing and till 4.00 hours post dose. The standard meals or snacks were served at check-in time and at 4.00, 8.00, 12.00, 24.00, 28.00, 32.00, 36.00, 48.00, 52.00, 56.00 and 60.00 hours (with a grace period of + 45 minutes) post dose and before check-out in each study period. The meal plan was uniform and identical in all the periods. Drinking water was not allowed for 1 hour before and 1 hour after dosing (except 240 mL of water given for administration of the drug). All subjects were dosed at the fixed time and advised to remain in sitting position for the first 2.00 hours following drug administration except clinically indicated/for natural exigency.

Sampling schedule and sample processing:

A total of 26 (1 × 5 mL) blood samples was collected from each subject as per the following schedule:

- Pre dose (00.00 hour) blood sample was collected within 1.50 hour prior to drug administration of each period and the post dose samples at 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 2.75, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 8.00, 10.00, 12.00, 16.00, 24.00, 36.00, 48.00 and 72.00 hours.
- Post study safety sample was collected after collection of 72.00-hour sample of the last period of the study.

The total volume collected per subject in this study was not exceed 300 mL including about 10 mL for screening, 260 mL for pharmacokinetic analysis, 22 mL for heparinized and about 08 mL for post study clinical assessment of lab parameters.

Blood samples were collected through an indwelling cannula placed in a forearm vein and transferred into pre-labeled K_2EDTA vacutainers. Post dose blood samples were collected within ± 2 minutes of specified sampling time during housing period.

The collected blood samples (i.e. from first blood sample collection at each time point) were placed in a refrigerated centrifuge and then spun at 4000 rpm for 10 minutes at 4ºC within 45 minutes, the plasma obtained from the blood samples were separated and transferred into two different polypropylene RIA vials (Aliquot 1of 2 and Aliquot 2 of 2). All samples were stored at a temperature of

-70±15°C at the clinical site until transferred on dry ice to analytical site after which was stored at a temperature of - 70±15°C.

Apremilast in human plasma was determined by using High Performance Liquid Chromatography with Tandem mass spectrometry with a Concentration range. of 1.009 – 802.593 ng/mL.

- **Population(s) studied**

A total of 38 male subjects (2 groups), aged 22-43 years, BMI 19.2 – 29.7 kg/m^2 were enrolled and dosed in the study. One subject was withdrawn due to an adverse event and 37 of them completed the study and were included in the pharmacokinetic and statistical analysis.

- **Analytical methods**

Apremilast in human plasma was determined by using High Performance Liquid Chromatography with Tandem mass spectrometry with a Concentration range of 1.009 – 802.593 ng/mL. The analytical method for Apremilast was developed and validated over a concentration range of 1.008– 806.223 ng/mL in BL-MV-495 at Bioanalytical laboratory. A total of 3918 plasma samples were received in two shipments.

A total of 3918 plasma samples were received in two shipments.

Analyte and ISTD were extracted by Liquid-Liquid Extraction with extraction solvent from human plasma. The mixture was vortexed centrifuged and the organic layer was transferred to tubes and evaporated. The residue was reconstituted with reconstitution solution and transferred to HPLC vials 15.0 µL was injected into AS 4000 system for analysis. The transition ions 461.200/257.100 (m/z) and 466.300/262.100 (m/z) were monitored for analyte and ISTD respectively. Data were acquired, integrated and processed by suitable software. Linear regression curve was obtained by using $1/x^2$ as a weighing factor. Concentrations ranging 1.009- 802.593 ng/mL for analyte were found to be linear with regression coefficient value ≥ 0.9992 (r). The lower limit of quantification (LLOQ) was 1.009 ng/mL using a plasma sample volume of 300.0 µL. Each Linearity curve contains STD Blk, STD Zero, 10 levels of CC standards and 5 levels of QC samples.

Study samples total storage period: 35 days at -70°C

- **Pharmacokinetic Variables**

Primary Efficacy Variables:

- C_{max}: Maximum observed plasma concentration following each treatment
- AUC_{0-t}: The area under the plasma concentration versus time curve from time zero to the last measurable concentration as calculated by linear trapezoidal method.

Secondary Efficacy Variables:

- AUC_{0-inf}: The area under the plasma concentration versus time curve from time zero to infinity. Where $AUC_{0-inf} = AUC_{0-t} + Ct/K_{el}$, Ct was the last measurable concentration and K_{el} was the terminal elimination rate constant
- T_{max}: Time of the maximum measured plasma concentration.
- $t_{1/2}$: The elimination half-life was calculated as $0.693/K_{el}$.
- K_{el}: First order rate constant associated with the terminal (log-linear) portion of the curve. This is estimated via linear regression of time vs. log concentration. This parameter was calculated

by linear least squares regression analysis using at least last three or more non-zero plasma concentration values

- $AUC\_{\%Extrap\_obs}$: The residual area in percentage was determined by the formula, $[(AUC_{0-inf}-AUC_{0-t})/AUC_{0-inf}] \times 100$.

- **Statistical methods**

The ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-t} of Apremilast was subjected to Analysis of Variance (ANOVA) using PROC GLM procedure in suitable software. ANOVA model was included Sequence, Formulation, Period and Subject (Sequence) as fixed effects. Sequence effect was tested using Subject (Sequence) as an error term.

The period, sequence and treatment/formulation effects was tested at 5% level of significance (alpha = 0.05).

Two one-sided test procedures for bioequivalence and 90 % confidence intervals for the ratio of geometric least squares mean between drug formulations was calculated, for ln-transformed data of C_{max} and AUC_{0-t} for Apremilast.

The power of a test to detect 20% difference between test and reference product was computed and reported for Apremilast.

Ratio of geometric least squares means of test and reference product was computed for ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-t} for Apremilast. Ratio analysis was reported for ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-t} for Apremilast.

Results

The results are summarised in Table 2 below. The test to reference ratio of geometric LS means and corresponding 90% confidence interval of the C_{max} and AUC_{0-t} were all within the bioequivalence acceptance range (Table 3).

Table 2 Pharmacokinetic parameters for apremilast (non-transformed values); N=37

Pharmacokinetic parameter	Test		Reference	
	geometric mean	SD	geometric mean	SD
$AUC_{(0-t)}$ hr*ng/ml	3926.398	1430.2955	3404.162	309.0711
$AUC_{(0-\infty)}$ hr*ng/ml	3957.016	1449.5390	3436.067	1319.6472
C_{max} ng/ml	451.372	102.1100	396.049	99.0557
T_{max}* hr	2.250	(0.750 - 5.000)	2.250	(0.500 - 4.500)
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours			
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity			
C_{max}	maximum plasma concentration			
T_{max}	time for maximum concentration (* median, range)			

Table 3 Statistical analysis for apremilast (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
$AUC_{(0-th)}$	116.57%	**110.83% – 122.62%**	12.9%
C_{max}	114.82%	**108.61% – 121.39%**	14.2%
* estimated from the Residual Mean Squares			

The test to reference ratio of geometric LS means and corresponding 90% confidence interval of the $AUC_{(0-t)}$ was within the acceptance range of 80-125%.

T_{max} was not observed in any of the subjects in the first sample time point. Concentrations for both reference and test drugs in pre-dose time point were BLLQ.

The LLOQ of 1.008 ng/mL was sensitive enough to detect levels of 5% of the minimum C_{max}.

- ***Safety data***

A total of five (05) Adverse events, (Four AEs during period-2 in-house and One AE during post study safety assessment) for subject numbers 06, 20, 31, 34 and 15 were reported in the entire study. Four AEs of subject numbers 06, 20, 31 and 34 were mild in nature and possibly related to the study drug. Reported post study adverse event for subject number 15 was mild in severity and possible related to the study drug.

No SAEs and deaths were reported during the study and in post study safety assessment. In this study, a single dose of test product (T) and reference product (R) were well tolerated in subjects under fasting condition. Based on the safety assessment, test product (T) are as safe as reference product (R).

Study C22175

According to the provided final study report, the study was conducted in the same clinical and bio-analytical facility, and was of the same design as the study C23132.

The following study results are reported:

Table 4 Pharmacokinetic parameters for apremilast (non-transformed values); N=34

Pharmacokinetic parameter	Test		Reference	
	arithmetic mean	SD	arithmetic mean	SD
$AUC_{(0-t)}$ h*ng/ml	3860.822	1307.3025	3163.576	1043.4622
$AUC_{(0-\infty)}$ h*ng/ml	3917.730	1330.0371	3217.658	1095.3263
C_{max} ng/ml	412.270	122.4054	493.052	129.7404
T_{max}* h	3.000	(0.750 - 5.000)	3.000	(0.500 – 5.000)
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours			
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity			
C_{max}	maximum plasma concentration			
T_{max}	time for maximum concentration (* median, range)			

Table 5 Statistical analysis for apremilast (ln-transformed values), N=34

Pharmacokinetic parameter	Geometric Mean				CV%*
	Test	Reference	Ratio T/R	90% Confidence Intervals	
$AUC_{(0-th)}$	3667.5810	2995.2678	122.45%	**114.69% – 130.73%**	12.9%
C_{max}	412.4275	335.2050	123.04%	**116.65% – 129.88%**	13.2%
* estimated from the Residual Mean Squares					

Since the parameters Cmax and AUC0 t did not meet the acceptance criteria, the study failed to prove bioequivalence.

Outlier analysis

The applicant provided a statistical outlier test for both studies (see Assessment of the responses) and found one outlier in each study. However, exclusion of outliers from bioequivalence analysis does not change conclusions on primary outcomes, i.e. study 22175 fails and study 23132 passes. It is concluded that outliers did not significantly biased primary outcomes of both studies.

Pooled analysis: Study C22175 + Study C23132

The pooling of the data was done with adjusted significance levels, using an adjusted coverage probability of 94.12%, according to the recommendations for two stage design study set in the bioequivalence guideline. The applicant suggested that ANOVA model observing interaction term study*treatment showed p-value >0.05, and concluded that pooling of data from two studies can be valid.

The pooled population consisted of 71 subjects, i.e. outliers are included.

The following results of pooled analysis are reported:

Table 6 Pharmacokinetic parameters for apremilast (non-transformed values); N=71

Pharmacokinetic parameter	Test		Reference	
	arithmetic mean	SD	arithmetic mean	SD
$AUC_{(0-t)}$ h*ng/ml	3894.995	1363.4061	3288.952	1187.1240
$AUC_{(0-\infty)}$ h*ng/ml	3938.203	1383.8155	3331.477	1213.7868
C_{max} ng/ml	439.830	112.1278	371.828	94.0471
T_{max}* h	2.750	(0. 050 - 5.000)	2.500	(0.500 – 5.000)
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours			
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity			
C_{max}	maximum plasma concentration			
T_{max}	time for maximum concentration (* median, range)			

Table 7 Statistical analysis for apremilast (ln-transformed values), N=71

Pharmacokinetic parameter	Geometric Mean				CV%
	Test	Reference	Ratio T/R	94.12% CI	
$AUC_{(0-t)}$	3684.1666	3089.1221	119.26%	**113.86% – 124.92%**	14.4%
C_{max}	426.9791	359.7849	118.68%	**113.55% – 124.04%**	13.8%

In addition, as requested in the D120 LoQ, the applicant provided the coverage probability of the confidence intervals that just meet the bioequivalence acceptance range (tipping point) for both primary endpoints. The coverage probability for AUC is 0.94236, and for Cmax is 0.97296.

Aizant Drug Research Solutions Pvt. Ltd. - Hyderabad
pooled_studies_C23132 and C22175 Analyte: Apremilast

Obs	name	vs	DF	Estimate	StdErr	testmean	refmean	tvalue	lo	hi	ratio	alpha	CoverProb
1	LnAUClast	T VS R	68	0.17648619	0.02416140	8.21145	8.03497	1.93107	113.864	124.999	119.302	94.12	0.94236
2	LnCmax	T VS R	68	0.17097361	0.02308611	6.05407	5.88310	2.25980	113.473	124.054	118.646	94.12	0.97296

Since the provided coverage probability is very close to what would be required for interim analysis with pre-defined alpha level, the strength of evidence is not considered sufficient to overcome the conflicting results from one failed and one successful trial.

3.3.2.2. Pharmacokinetic Conclusion

Based on the presented data, bioequivalence between Apremilast Viatris 30 mg film-coated tablets and Otezla 30 mg film-coated tablets, Amgen Europe BV cannot be concluded.

3.3.2.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

3.3.3. Discussion on clinical pharmacology

This application concerns a generic version of apremilast film-coated tablets. The reference product Otezla is indicated for the treatment of psoriatic arthritis, psoriasis and Behçet's disease. No non-clinical studies have been provided for this application but an adequate summary of the available non-clinical information for the active substance was presented and considered sufficient.

From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature is considered sufficient.

The bioequivalence study forms the pivotal basis with a randomized, two-period, two-treatment, two-sequence, single-dose, cross-over study. The study design is considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. According to the SmPC of the reference product Otezla, no specific recommendation regarding food intake is given for apremilast posology since it can be taken with or without food. Therefore, the conduct of the single dose study under fasting conditions as most sensitive conditions to detect a potential *in-vivo* difference between formulations is considered adequate. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was well validated. Pharmacokinetic and statistical methods applied are adequate.

The applicant conducted two identically designed bioequivalence studies, of which the first failed (study C22175) and another (study C23132) succeeded to prove bioequivalence. However, the applicant should clarify why the second study was started before the initial study had completed even if both completed within a day.

Two outliers have been observed, one in each study. Subject No.12 was an outlier in study C22175 and subject No.35 was an outlier in study C23132. The analysis of bioequivalence have been conducted with and without each of them separately for the two studies. The results showed no difference in the bioequivalence conclusion. The results indicate that the outliers in both studies did not have significant impact on the bioequivalence results. Since the applicant failed to justify that the study C22175 is irrelevant, meta-analysis of two studies is logical and applicable solution in order to explore the whole body of existing evidence. This is because positive BE study does not necessary contradict the earlier study but instead adds new data that allows one to be confident that the earlier failure was due to a lack of information rather than a lack of bioequivalence. However, according to the EMA BE guideline, the plan to employ a two-stage design must be indicated in the protocol of a study together with the adjusted significance levels to be used for each of the analyses. Even though two-stage approach allows for analysis of two separate samples, the limitation is that it was employed in retrospect. The very first study was intended to serve as a pivotal study and did not envisage this design. Regarding the type-1-error control in the pooled analysis, overall acceptable type I error had already been spent in the first study (i.e. study C22175 was evaluated using a confidence interval with 90% coverage probability), and there was no a priori concept of adequate handling of the type-1-error for the subsequent tests.

Statistical analysis evaluating heterogeneity between the two studies showed that study*treatment interaction is not statistically significant, i.e. study*treatment term p-value is greater than the 0.05. Therefore, the pooling of the studies can be acceptable.

Regarding the statistical analysis of pooled data from the two studies, the applicant submited the requested raw data used to calculate the pooled estimates of AUC_{0-t} and C_{max}. The pooled analysis for two studies were conducted with same inclusion and exclusion criteria at same clinical facility and only added one-time point 72.00 hour additionally in the study C23132In the bioequivalence analysis of the pooled data conducted by the applicant the model without study*treatment term was used, which is the model suggested by the MWP.

According to the analysis, the point estimate of the geometric mean ratio and their 94.12%CI for both PK parameters lie entirely within the conventional acceptance range 80.00-125.00%. The coverage probabilities for AUC (94.24%) and Cmax (97.30%) are calculated. The results across the 2 studies and the pooled analysis are consistently showing a somewhat higher bioavailability for the test product i.e. Study C22175 AUC(0-t) 122.45% (90%CI 114.69 – 130.73); Study C23132 AUC(0-t) 116.57% (90%CI 110.83 – 122.62); and for the pooled analysis AUClast 119.30 (94.12% CI 113.86 – 124.99). In view of CHMP, the post-hoc adjusted coverage probability of 94.12% for the pooled analysis is not accepted for decision-making as it does not effectively provide type I error control (which has already been spent after one failed study). In order to minimize type I error inflation, the coverage probability of the confidence intervals in the pooled analysis should be statistically compelling, i.e. much larger than conventionally accepted for pre-planned analyses. Since the provided coverage probability is very close to what would be required for interim analysis with pre-defined alpha level, the strength of evidence is not considered sufficient to overcome the conflicting results from one failed and one successful trial.

Similarity of dissolution profiles was proven for both lower strengths with the bio-batch of the highest strength in all media used by calculating the f_2 (>50). Since the RSD values for the dissolution results for the 10 mg strength in medium 0.1N HCl and pH 6.8 were above 20%, the applicant used the Bootstraping method to estimate similarity with 30 mg strength. The results of the bootstrapping method indicate the similarity between the bio-batch and the 10 mg strength. Therefore, biowaiver for 10 mg strength can be granted.

No new studies were submitted, and none are required for generic applications.

No post-marketing data are available. The medicinal product has not been marketed in any country.

3.3.4. Clinical efficacy

N/A

3.3.5. Discussion on clinical efficacy

N/A

3.3.6. Clinical safety

N/A

3.3.7. Post marketing experience

N/A

3.3.8. Discussion on clinical safety

N/A

3.3.9. Conclusions on clinical aspects

Based on the presented data consisting of two bioequivalence studies (one of them failed), Apremilast Viatris 30 mg film-coated tablets currently cannot be considered bioequivalent with Otezla 30 mg film-coated tablets Amgen Europe BV.

The biowaiver for Apremilast Viatris 10 mg and 20 mg strength is acceptable, however bioequivalence for 30 mg strength still needs to be demonstrated.

3.4. Risk management plan

3.4.1. Safety specification

Risk management plan version no. 0.1 has been submitted with DLP date of 29-Aug-2023 and Date of final sign off 29-Sep 2023.

Product overview is presented in the table below :

Active Substance(s) (INN or Common Name)	Apremilast
Pharmacotherapeutic Group(s) (ATC Code)	Immunosuppressant's, selective immunosuppressants. ATC code: L04AA32
Marketing Authorisation Holder	Viatris Limited, Ireland
Medicinal Products to Which this RMP Refers	1
Invented Name(s) in the European Economic Area (EEA)/UK	Apremilast Viatris
Marketing Authorisation Procedure	Centralized (EMA/H/C/006193)
Brief Description of the Product	Chemical class Apremilast(N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-1,3-dioxoisoindol-4-yl]acetamide, is a novel oral small-molecule inhibitor of phosphodiesterase 4 (PDE4), works intracellularly to modulate a network of pro-inflammatory and anti-inflammatory mediators. Summary of mode 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. Important information about its composition: Not applicable
Hyperlink to the Product Information:	PI available in section 1.3.1 of the dossier

<table>
<tr><td>Indication(s) in the EEA</td><td><u>Current:</u>

<u>Psoriatic arthritis</u>
Apremilast Viatris, 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.

<u>Psoriasis</u>
Apremilast Viatris 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).

<u>Behçet's disease</u>
Apremilast Viatris is indicated for the treatment of adult patients with oral ulcers associated with Behçet's disease (BD) who are candidates for systemic therapy.

<u>Proposed</u>:
None</td></tr>
<tr><td>Dosage in the EEA</td><td><u>Current:</u>
The recommended dose of apremilast is 30 mg taken orally twice daily, approximately 12 hours apart (morning and evening), with no food restrictions. An initial titration schedule is required as shown below in Table. No re-titration is required after initial titration.

<table>
<tr><th>Day 1</th><th colspan="2">Day 2</th><th colspan="2">Day 3</th><th colspan="2">Day 4</th><th colspan="2">Day 5</th><th colspan="2">Day 6 & therefore</th></tr>
<tr><td>AM</td><td>AM</td><td>PM</td><td>AM</td><td>PM</td><td>AM</td><td>PM</td><td>AM</td><td>PM</td><td>AM</td><td>PM</td></tr>
<tr><td>10 mg</td><td>10 mg</td><td>10 mg</td><td>10 mg</td><td>20 mg</td><td>20 mg</td><td>20 mg</td><td>20 mg</td><td>30 mg</td><td>30 mg</td><td>30 mg</td></tr>
</table>

If patients miss a dose, the next dose should be taken as soon as possible. If it is close to the time for their next dose, the missed dose should not be taken and the next dose should be taken at the regular time.

During pivotal trials the greatest improvement was observed within the first 24 weeks of treatment for PsA and PSOR and within the first 12 weeks of treatment for BD. If a patient shows no evidence of therapeutic benefit after this time period, treatment should be reconsidered. The patient's response to treatment should be evaluated on a regular basis.

<u>Proposed</u>:
None</td></tr>
</table>

Pharmaceutical Form(s) and Strengths	<u>Current:</u> Apremilast Viatris 10 mg film-coated tablets Apremilast Viatris 20 mg film-coated tablets Apremilast Viatris 30 mg film-coated tablets <u>Proposed</u>: None
Is/Will the Product Be Subject to Additional Monitoring in the EU	No

SI to SVI are not applicable for the product.

The Safety Specification (Part II, SVIII) from RMP version 0.1, dated 29-Sep-2023 is assessed below:

Summary of safety concerns

Table 8 Summary of safety concerns

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

CHMP comment:

The safety concerns for the reference medicinal product (Otezla: EPAR - Risk Management Plan Summary, version 14.1 dated: 04 Nov 2021) have been adopted by the MAH.

The Rapporteur agrees that the safety concerns listed by the applicant are appropriate.

3.4.2. Discussion on safety specification

The safety concerns listed by the applicant are in line with the reference medicinal product.

3.4.3. Conclusions on the safety specification

Having considered the data in the safety specification,

- It is agreed that the safety concerns listed by the applicant are appropriate.

Pharmacovigilance plan

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond ADRs reporting and signal detection:

Specific adverse reaction follow-up questionnaires for:

- Serious events of hypersensitivity
- Suicidality
- Serious events of depression
- Vasculitis

- Malignancies
- 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.

The forms are provided in Annex 4 Specific Adverse Drug Reaction Follow-up Forms of the RMP.

III.2 Additional pharmacovigilance activities

As current routine pharmacovigilance activities are sufficient, no additional pharmacovigilance activities are recommended.

III.3 Summary Table of Additional Pharmacovigilance Activities

None.

CHMP assessment comment:

Note that, this RMP section should describe the list of questionnaires by type of activity and not by safety concern according to the guidance on the format of the RMP ***(RSI)****.*

The applicant is remained that as per GVP V, in order to deliver a consistent message and provide useful data for the analysis of the reports, the questions in the follow-up questionnaires should be kept as similar as possible with those from the innovator. The routine pharmacovigilance activities proposed by the applicant are in line with the innovator and therefore endorsed.

The applicant stated that no additional pharmacovigilance (PhV) activities are proposed, which is endorsed.

Please refer to the D94 PRAC Rapp RMP AR.

Risk minimisation measures

Routine Risk Minimisation Measures

Not applicable.

Additional risk minimisation measures

Not applicable.

3.1. Summary of the Risk Minimisation Measures

Table 9 Part V.3 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		
Serious events of hypersensitivity	Routine risk minimization measures: SmPC Contraindicated in those with hypersensitivity to apremilast (Section 4.3) and the risk of hypersensitivity is presented in Section 4.8. PIL Includes advice not to take if allergic to apremilast in Section 2 and included in Section 4. Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Event specific questionnaire for the collection of the adverse event and follow-up Additional pharmacovigilance activities: None
Suicidality	Routine risk minimization measures:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		
	SmPC The risk of triggering suicide is discussed in Sections 4.4 and 4.8. PIL Included in Sections 2 and 4 of the patient information. Additional risk minimization measures: None	Event specific questionnaire for the collection of the adverse event and follow-up Additional pharmacovigilance activities None
Serious events of depression	Routine risk minimization measures: SmPC The risk of depression is discussed in Sections 4.4 and 4.8. PIL Included in Sections 2 and 4 of the patient information. Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Event specific questionnaire for the collection of the adverse event and follow-up Additional pharmacovigilance activities: None
Important Potential Risks		
Vasculitis	Routine risk minimization measures: None Additional risk minimization: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Event specific questionnaire for the collection of the adverse event and follow-up Additional pharmacovigilance activities: None
Malignancies	Routine risk minimization measures: None Additional risk minimization: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Event specific questionnaire for the collection of the adverse event and follow-up

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		
		Additional pharmacovigilance activities: None
Serious events of anxiety and nervousness	Routine risk minimization measures: None Additional risk minimization: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Serious infections including opportunistic infections and transmission of infections through live vaccines	Routine risk minimization measures: None Additional risk minimization: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Event specific questionnaire for the collection of the adverse event and follow-up Additional pharmacovigilance activities: None
Major adverse cardiac event (MACE) and tachyarrhythmia	Routine risk minimization measures: None Additional risk minimization: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Event specific questionnaire for the collection of the adverse event and follow-up Additional pharmacovigilance activities: None
Prenatal embryo-fetal loss and delayed fetal development (reduced ossification and fetal weight) in pregnant women exposed to apremilast	Routine risk minimization measures: <u>SmPC</u> Contraindicated in pregnancy (Section 4.3). Includes information regarding use in pregnancy (Section 4.6) and preclinical information on embryo-fetal development (Section 5.3). <u>PIL</u>	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Event specific questionnaire for the collection of the adverse event and follow-up Additional pharmacovigilance activities: None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		
	Includes information regarding use in pregnancy (including do not take if pregnant) in Section 2. Additional risk minimization measures: None	
Missing Information		
Long-term safety	Routine risk minimization measures: None Additional risk minimization: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

CHMP assessment comment:

In line with the originator, routine risk minimisation activities are sufficient to manage the safety concerns of the reference medicinal product. Therefore, a statement indicating that the safety information in the product information of the generic product is aligned with the originator product is sufficient for RMP part V. The applicant should update this statement instead of "not applicable" in the section of routine risk minimisation measures. In addition, Table 4 should be also replaced by this statement ***(RSI).*** *Of note, the safety concerns are wrongly classified in the table 4 presented.*

Please refer to the D94 PRAC Rapp RMP AR.

Conclusion on the RMP

The RMP could be acceptable provided an updated RMP and satisfactory responses to the list of questions below is submitted.

Pharmacovigilance

Pharmacovigilance system

The Pharmacovigilance System Master File contains details of the system and processes that the applicant has in place to identify and/or characterize the risks recognised in the safety specification.

Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond ADRs reporting and signal detection:

Specific adverse reaction follow-up questionnaires for:

• Serious events of hypersensitivity

• Suicidality

• Serious events of depression

• Vasculitis

• Malignancies

• 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.

These questionnaires were provided in the Annex 4 of the RMP and are in line with the reference product, Otezla

Additional Pharmacovigilance Activities

As current routine pharmacovigilance activities are sufficient, no additional pharmacovigilance activities are recommended.

The Rapporteur considers that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

CHMP comment

Submitted RMP is in line with the GVP Module V, Rev. 2.

Product overview is in line with the reference product, Otezla Risk Management Plan Summary, version 14.1 dated: 04 Nov 2021. List of safety concerns is aligned with the reference product. Routine pharmacovigilance activities are described by the applicant and are deemed sufficient.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

4. Benefit risk assessment

This application concerns a generic version of apremilast film-coated tablets. The reference product Otezla is indicated for psoriatic arthritis, psoriasis and Behçet's disease. No nonclinical studies have been provided for this application but an adequate summary of the available non-clinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature is considered sufficient.

The bioequivalence study C23132 is presented by the applicant as the pivotal prove of therapeutic equivalence between this generic and the reference medicinal product. The study design is considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied are adequate.

However, the applicant has also conducted another BE study C22175 whose results failed to demonstrate BE. Additionally, study report for this study was provided as well as pooled analysis of the data from both BE studies. According to the provided raw data, the point estimate of the geometric mean ratio and their 94.12% CI for both PK parameters lie entirely within the conventional acceptance range 80.00-125.00%. However, the post-hoc adjusted coverage probability of 94.12% for the pooled analysis is not accepted for decision-making as it does not effectively provide type I error control (which has already been spent after one failed study). In order to minimize type I error inflation, the coverage probability of the confidence intervals in the pooled analysis should be statistically compelling, i.e. much larger than conventionally accepted for pre-planned analyses. Since the provided coverage probability is very close to what would be required for interim analysis with pre-defined alpha level, the strength of evidence is not considered sufficient to overcome the conflicting results from one failed and one successful trial.

BE between Apremilast Viatris 30 mg film-coated tablets and Otezla 30 mg film-coated tablets cannot be concluded at the current stage. Moreover, there are minor issues that still need to be answered.

The biowaiver for Apremilast Viatris 10 mg and 20 mg strength is acceptable, however bioequivalence for 30 mg strength still needs to be demonstrated.

4.1. Conclusions

The overall benefit /risk balance of Apremilast Viatris is currently negative due to the quality MO and clinical MO.