COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Tolreso 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg and 25 mg hard capsules (lenalidomide)

NL/H/5136/001-007/DC

Date: 20 September 2021

This module reflects the scientific discussion for the approval of Tolreso 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg and 25 mg hard capsules. The procedure was finalised at 2 June 2021. 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
BCS	Biopharmaceutics classification system
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
ERA	Environmental Risk Assessment
FL	Follicular lymphoma
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MCL	Mantle cell lymphoma
MDS	Myelodysplastic syndromes
MM	Multiple myeloma
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
PPP	Pregnancy prevention program
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
SPM	Second primary malignancy
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 Tolreso 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg and 25 mg hard capsules, from Acino AG.

The products are indicated for the treatment of:

- Multiple myeloma (MM)

Tolreso as monotherapy is indicated for the maintenance treatment of adult patients with newly diagnosed multiple myeloma who have undergone autologous stem cell transplantation.

Tolreso as combination therapy with dexamethasone, or bortezomib and dexamethasone, or melphalan and prednisone (see section 4.2 of the SmPC) is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant.

Tolreso in combination with dexamethasone is indicated for the treatment of multiple myeloma in adult patients who have received at least one prior therapy.

- Myelodysplastic syndromes (MDS)

Tolreso as monotherapy is indicated for the treatment of adult patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate.

- Mantle cell lymphoma (MCL)

Tolreso as monotherapy is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (see sections 4.2 and 5.1 of the SmPC).

- Follicular lymphoma (FL)

Tolreso in combination with rituximab (anti-CD20 antibody) is indicated for the treatment of adult patients with previously treated follicular lymphoma (Grade 1 – 3a).

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator products Revlimid 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg and 25 mg hard capsules by Bristol-Myers Squibb Pharma EEIG, which has been registered in the European Economic Area (EEA) via a centralised procedure (EMEA/H/C/000717). The 5 mg, 10 mg, 15 mg and 25 mg strengths have been authorised since 19 June 2007, the 2.5 mg and 7.5 mg strengths since 10 September 2012, and the 20 mg strength has been authorised since 23 February 2015.

The concerned member state (CMS) involved in this procedure was France.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

Orphan similarity

The MAH has submitted an orphan similarity assessment report that addresses the possible similarity between Tolreso and the orphan medicinal products which have received a marketing authorisation.

For the similarity assessment the following criteria were considered:

- principal molecular structural features
- mechanism of action
- therapeutic indications

The reference product Revlimid (lenalidomide, EU/1/07/391) was authorised with orphan indications. However, for all indications the market exclusivity has expired, or has been withdrawn upon request of the MAH of Revlimid. Thus, Revlimid itself is no longer an orphan medicine.

For the orphan indication Multiple Myeloma/Plasma Cell Myeloma the MAH provided a similarity assessment versus:

Tradename (act. subst.):	**Orphan design. nr:**	**Date:**	**Expiry orphan status:**
Imnovid (pomalidomide)	EU/3/09/672	08/08/2013	08/08/2023
Farydak (panobinostat)	EU/3/12/1063	01/09/2015	01/09/2025
Kyprolis (carfilzomib)	EU/3/08/548	23/11/2015	23/11/2025
Darzalex (daratumumab)	EU/3/13/1153	24/05/2016	24/05/2026
Ninlaro (ixazomib)	EU/3/11/899	23/11/2016	23/11/2026
BlenRep (belantamab mafodotin)	EU/3/17/1925	26/08/2020	26/08 2030

For the orphan indication Myelodysplastic syndrome the MAH provided a similarity assessment versus:

Tradename (act. subst.):	**Orphan design. nr:**	**Date:**	**Expiry orphan status:**
Reblozyl (luspatercept)	EU/3/14/1331	26/06/2020	26/06/2030

For the orphan indication Mantle cell lymphoma the MAH provided a similarity assessment versus:

Tradename (act. subst.):	**Orphan design. nr:**	**Date:**	**Expiry orphan status:**
Imbruvica (ibrutinib)	EU/3/13/1115	21/10/2014	21/10/2024
Tecartus	EU/3/19/2220	15/12/2020	15/12/2030

For the orphan indication Follicular lymphoma the MAH provided a similarity assessment versus:

Tradename (act. subst.):	Orphan design. nr:	Date:	Expiry orphan status:
Gazyvaro (obinutuzumab)	EU/3/15/1504	23/07/2014	23/07/2024

Considering the above mentioned criteria, it has been agreed that Tolreso are not similar to any authorised orphan medicinal product.

II. QUALITY ASPECTS

II.1 Introduction

Tolreso are hard capsules that differ in appearance according to their strength:

- 2.5 mg: Blue- green coloured cap and white coloured, “2.5 mg” printed body with black ink, hard gelatine capsule filled with white to off-white colour powder.
- 5 mg: White coloured cap and white coloured, “5 mg” printed body with black ink, hard gelatine capsule filled with white to off-white colour powder.
- 7.5 mg: Pale yellow coloured cap and white coloured, “7.5 mg” printed body with black ink, hard gelatine capsule filled with white to off-white colour powder.
- 10 mg: Blue-green coloured cap and pale yellow coloured, “10 mg” printed body with black ink, hard gelatine capsule filled with white to off-white colour powder.
- 15 mg: Pale blue coloured cap and white coloured, “15 mg” printed body with black ink, hard gelatine capsule filled with white to off-white colour powder.
- 20 mg: Blue-green coloured cap and pale blue coloured, “20 mg” printed body with black ink, hard gelatine capsule filled with white to off-white colour powder.
- 25 mg: White coloured cap and white coloured, “25 mg” printed body with black ink, hard gelatine capsule filled with white to off-white colour powder.

The capsules contain as active substance 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg or 25 mg of lenalidomide, respectively.

The hard capsules are packed in polyvinylchloride (PVC)/polychlorotrifluoroethylene (PCTFE) - aluminium foil blisters in carton boxes.

The excipients are:
Capsule contents – lactose anhydrous, microcrystalline cellulose, croscarmellose sodium and magnesium stearate.
Capsule shell - gelatine, titanium dioxide, indigo carmine (2.5, 10, 15 and 20 mg products) and yellow iron oxide (2.5, 7.5, 10 and 20 mg products).
Printing ink - shellac, black iron oxide, propylene glycol, potassium hydroxide and concentrated ammonia solution.

II.2 Drug Substance

The active substance is lenalidomide, an established active substance, which is not described in any Pharmacopoeia. Lenalidomide is a white to off-white, light yellow or light grey crystalline powder. It is freely soluble in dimethyl sulfoxide, slightly soluble in methanol and very slightly soluble in water. Lenalidomide has one chiral centre and it is used as racemic mixture. Since it is a mixture of two enantiomers, it shows no optical rotation. Lenalidomide exhibits several polymorphic forms. The drug substance manufactured has polymorphic form A.

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

The manufacturing process consists of two synthetic steps where crystallisation, recrystallisation and slurry processes are applied for isolation and/or purification of the active substance. No recovery, blending of batches or micronisation are applied. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised.

Quality control of drug substance

The active substance specification has been established in-house by the MAH and is identical to that of the ASMF-holder. The specification is acceptable in view of the route of synthesis and various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for six production-scale batches.

Stability of drug substance

Stability data on the active substance have been provided for six production-scale batches, stored at 25°C/60% RH (twelve months) and 40°C/75% RH (six months). The drug substance was stored in a Low Density Polyethylene (LDPE) in a High Density Polyethylene (HDPE) bag in an aluminium-PE bag in a fibre drum. No changes in appearance, identification (polymorphic form), water content, assay, related substances, particle size distribution or microbiological quality were observed in long-term and accelerated conditions. Photostability studies that were performed in line with the relevant ICH guideline showed that the drug substance is not photosensitive. Based on the data submitted, a retest period could be granted of twelve months without any storage restrictions.

II.3 Medicinal Product

Pharmaceutical development

The products are established pharmaceutical forms and their development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions are explained. The quality by design approach was used to develop the formulation and manufacturing process. The main development studies concerned the characterisation of the reference products, optimisation of the formulation, the manufacturing process optimisation and dissolution method development.

A biopharmaceutics classification system (BCS)-based biowaiver has been requested, therefore, comparative multimedia dissolution profiles of the test- and reference product have been provided for all strengths. The justification of the BCS-based biowaiver and the biowaiver for additional strengths will be discussed in section IV on Clinical aspects.

Manufacturing process

The products are manufactured using conventional manufacturing techniques. The manufacturing process consists of dry mixing and encapsulation. The description of the manufacturing process is acceptable. The manufacturing process has been adequately validated according to relevant European guidelines. Four blend batches of the minimum and maximum blend batch size were used for validation and at least two batches of the filled capsules of each strength.

Control of excipients

All excipients are of Pharmacopoeial grade (European, United States (US) or US-National Formulary (NF)) and/or are in accordance with Commission Regulation 231/2012. The specifications of the excipients 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 description, identification, disintegration, water content, uniformity of dosage units, assay, dissolution, related substances and microbiological quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. A risk assessment regarding elemental impurities, in line with ICH Q3D, has been provided.

Satisfactory validation data for the analytical methods have been provided. Batch analytical data from at least two batches per strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three batches of the 2.5 mg, 7.5 mg, 10 mg and 25 mg products and of two batches of the 5 mg, 15 mg and 20 mg products, stored at 25°C/60% RH (18 months) and 40°C/75% RH (six months). The conditions used in the stability studies are according to the ICH stability guideline and the batches were stored in

the proposed commercial packaging. Based on the data submitted, a shelf life was granted of 30 months. The labelled storage conditions are: "Store in the original package. This medicinal product does not require any special temperature storage conditions."

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM 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.

II.4 Discussion on chemical, pharmaceutical and biological aspects

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

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

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

III.2 Discussion on the non-clinical aspects

These products are generic formulations of Revlimid, which are available on the European market. Reference is made to the preclinical data obtained with these innovator products. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is 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

Lenalidomide is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required. The MAH requested a BCS-based biowaiver for Tolreso 25 mg, and a biowaiver for the additional strengths, which will be discussed below.

IV.2 Pharmacokinetics

BCS-based biowaiver

According to the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **), "a BCS-based biowaiver approach is meant to reduce *in vivo* bioequivalence studies, i.e., it may represent a surrogate for *in vivo* bioequivalence. *In vivo* bioequivalence studies may be exempted if an assumption of equivalence in *in vivo* performance can be justified by satisfactory *in vitro* data. Applying for a BCS-based biowaiver is restricted to highly soluble drug substances with known human absorption and considered not to have a narrow therapeutic index. The concept is applicable to immediate release, solid pharmaceutical products for oral administration and systemic action having the same pharmaceutical form."

The MAH has requested a BCS-based biowaiver for the 25 mg lenalidomide product. Therefore, comparative dissolution data between two batches of the 25 mg test product and one batch of the 25 mg reference product were provided. For this immediate release drug product, the following requirements for a BCS-based biowaiver have been met:

- The drug substance should exhibit high solubility and complete absorption (BCS-class I substance).

According to EMA/CHMP/177335/2016/Corr., lenalidomide is a compound with complete absorption but the available data on solubility do not allow for a BCS-I classification. Therefore, the MAH has provided adequate solubility data demonstrating the high solubility of the drug substance (the highest strength, 25 mg, is completely dissolved in 250 ml of aqueous media in the pH range of 1.2 - 6.8).

- Very rapid or similarly rapid (at least 85% in 30 minutes) *in vitro* dissolution has to be demonstrated.

It was observed that more than 85% of the drug substance in both the proposed product and reference product is dissolved within 15 minutes in quality control (QC) medium and aqueous media with pH's ranging from 1.2-6.8. The dissolution tests have been performed in usual experimental conditions. The dissolution profiles can be considered as similar.

- Excipients that might affect bioavailability are qualitatively and quantitatively the same, however, it could be acceptable if excipients not affecting bioavailability are qualitatively the same and quantitatively very similar.

The excipients in the proposed product are based on those in the reference product, thus the qualitative composition is the same. The quantitative compositions of the test and reference product are different. However, the MAH has adequately considered that it is highly unlikely that the chosen excipients affect the gastrointestinal transit time. In line with the assessment of the BCS-based biowaiver, the excipients and their levels are acceptable.

In conclusion, the 25 mg lenalidomide product fulfils all conditions for a BCS-based biowaiver, which has therefore been granted.

Biowaiver of additional strengths

For the 2.5, 5, 7.5, 10, 15 and 20 mg strengths, a biowaiver was requested based on dose-proportionality and the comparative dissolution profiles of the 25 mg batch used in the BCS-based biowaiver assessment and two batches of all other strengths.

The different product strengths comply with the following biowaiver criteria from CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **:

- The different product strengths are manufactured by the same manufacturing process;
- The products have the same qualitative composition;
- The products are quantitatively proportional;
- Appropriate *in vitro* dissolution data have confirmed the adequacy of waiving additional *in vivo* bioequivalence testing. The used dissolution method is acceptable in view of the recommendations for dissolution methods for biowaivers of additional strengths. For the 25 mg BCS-based biowaiver test batch and for two batches of all other strengths, the dissolution is more than 85% in 15 minutes in QC medium and buffers at pH 1.2, pH 4.5 and pH 6.8.

Therefore, similarity can be accepted and a biowaiver for the additional strengths has been granted.

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 Tolreso.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	• Teratogenicity • Serious infection due to neutropenia

	• Second primary malignancy (SPM) • Tumour flare reaction (only for mantle cell lymphoma and follicular lymphoma)
Important potential risks	• Cardiac failure • Cardia arrhythmias • Ischaemic heart disease (including myocardial infarction) • Off-label use
Missing information	None

Further, the MAH committed to perform additional risk minimisation measures pursuant to Article 21a/22 of Directive 2001/83/EC, which are summarised in table 2. In each Member State, the MAH shall agree the content, format and distribution of the educational material with the national competent authority. In line with the reference products, the risk minimisation materials should be part of the conditions to the marketing authorisation. For all other safety concerns, routine risk minimisation measures are considered sufficient for these products.

Table 2. Summary table of additional risk minimisation measures

Safety concern	Additional risk minimisation measures

Teratogenicity	• Pregnancy prevention program (PPP)
	• Educational materials for healthcare professionals
	  ○ Guide for healthcare professionals
	  ○ Checklist for physicians
	• Educational materials for patients
	  ○ Guide for female patients with childbearing potential and their partners
	  ○ Guide for female patients without childbearing potential
	  ○ Guide for male patients
	  ○ Patient safety card
	• Controlled distribution

Serious Infection due to neutropenia	• None

SPM	• Educational materials for healthcare professionals
	  ○ Guide for healthcare professionals
	  ○ Checklist for physicians

Cardiac Failure and Cardiac Arrhythmias	• None
Ischaemic Heart Disease (Including Myocardial Infarction)	• None
Off-label use	• None

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator products Revlimid. No new clinical studies were conducted. A BCS-based biowaiver has been granted for the 25 mg product; for the additional strengths, a biowaiver

has been granted. Risk management is adequately addressed, and additional risk minimisation measures are taken. These generic medicinal products can be used instead of the reference products.

V. USER CONSULTATION

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 Lenalidomide Devatis (NL/H/4989/001-007). 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

Tolreso 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg and 25 mg hard capsules have a proven chemical-pharmaceutical quality and are generic forms of Revlimid 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg and 25 mg hard capsules. Revlimid are well-known medicinal products with established favourable efficacy and safety profiles. The benefit/risk balance is considered positive.

The Board followed the advice of the assessors.

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 Tolreso with the reference products, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 2 June 2021.

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