COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Lenalidomide Devatis 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg and 25 mg, hard capsules

(lenalidomide)

NL/H/4989/001-007/DC

Date: 14 January 2021

This module reflects the scientific discussion for the approval of Lenalidomide Devatis 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg and 25 mg, hard capsules. The procedure was finalised at 15 October 2020. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

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

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Lenalidomide Devatis 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg and 25 mg, hard capsules, from Devatis GmbH.

The product is indicated for:
Multiple myeloma
Lenalidomide Devatis as monotherapy is indicated for the maintenance treatment of adult patients with newly diagnosed multiple myeloma who have undergone autologous stem cell transplantation.

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

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

Follicular lymphoma
Lenalidomide Devatis 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 product Revlimid 5 mg, 10 mg, 15 mg and 25 mg hard capsules (EU/1/07/391) which has been registered in the EEA by Celgene Europe B.V. since 19 June 2006. Revlimid 2.5 mg and 7.5 mg have been registered 10 September 2012. Revlimid 20 mg has been registered 23 February 2015.

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

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

Similarity assessment in view of the orphan drug legislation
The MAH provided a similarity assessment report versus the following orphan medicinal products:

Multiple Myeloma/Plasma Cell Myeloma

Tradename (act. subst.):	Orphan design. nr:	Date:	Expiry orphan status:
Ninlaro (ixazomib)	EU/3/11/899	23/11/2016	23/11/2026

Kyprolis (carfilzomib)	EU/3/08/548	23/11/2015	23/11/2025
Farydak (panobinostat)	EU/3/12/1063	01/09/2015	01/09/2025
Imnovid (pomalidomide)	EU/3/09/672	08/08/2013	08/08/2023
Darzalex (daratumumab)	EU/3/13/1153	24/05/2016	24/05/2026
Blenrep (belantamab mafodotin)	EU/3/17/1925	11/09/2020	11/09/2030

Follicular lymphoma

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

It is concluded that, having considered the arguments presented by the MAH of Lenalidomide Devatis, the indication and mechanism of action of lenalidomide and the other active substances are not similar in the context of orphan medicinal products. Lenalidomide Devatis is not considered identical (as defined in Article 3 of Commission Regulation (EC) No. 847/2000) to the products listed above.

II. QUALITY ASPECTS

II.1 Introduction

Lenalidomide Devatis is a hard capsule with black imprints and filled with a white to off-white powder:
2.5 mg – White body imprinted with “2.5 mg” with a blue-green cap imprinted with “DEVA”
5 mg - White body imprinted with “5 mg” with a white cap imprinted with “DEVA”
7.5 mg - White body imprinted with “7.5 mg” with a pale yellow cap imprinted with “DEVA”
10 mg – Pale yellow body imprinted with “10 mg” with a blue-green cap imprinted with “DEVA”
15 mg - White body imprinted with “15 mg” with a pale blue cap imprinted with “DEVA”
20 mg – Pale blue body imprinted with “20 mg” with a blue-green cap imprinted with “DEVA”
25 mg - White body imprinted with “25 mg” with a white cap imprinted with “DEVA”

The product contains as active substance 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg or 25 mg of lenalidomide.

The hard capsule is packed in oPA/Al/PVC/Al blisters.

The excipients are:
Capsule contents
- Lactose, anhydrous
- microcrystalline cellulose (E460(i))
- Croscarmellose sodium (E468)
- Magnesium stearate (470b)

Capsule shell
- Gelatin
- Titanium dioxide (E171)
- Only 2.5 mg, 10 mg, 15 mg, 20 mg: Indigotine (E132)
- Only 2.5 mg, 7.5 mg, 10 mg, 20 mg: Yellow iron oxide (E172)

Printing ink
- Shellac
- Propylene glycol
- Black iron oxide (E172)
- Potassium hydroxide
- concentrated ammonia solution

The seven tablet strengths are dose proportional.

II.2 Drug Substance

The active substance is lenalidomide, an established active substance that is not described in the European Pharmacopoeia (Ph.Eur.). The drug substance is very slightly soluble in water. It has one chiral center and is manufactured as a racemate. Crystalline form-A of the drug substance is consistently manufactured.

The Active Substance Master File (ASMF) procedure is used by both manufacturers 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 MAH 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 a two-step synthesis with the starting materials. The specifications for the proposed starting materials are considered acceptable. Acceptable specifications have also been adopted for solvents and reagents.

Quality control of drug substance

The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for six production scaled batches.

Stability of drug substance
Stability data on the active substance have been provided for six production scaled batches stored at 25°C/60% RH (12 months) and 40°C/75% RH (6 months). Based on the data submitted, a retest period could be granted of 12 months.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The main development studies concerned the characterisation of the reference product, optimisation of the formulation, the manufacturing process optimisation and dissolution method development.
A BCS-based biowaiver is applied for all strengths and comparative, multimedia dissolution profiles of the test- and reference product have been provided for all seven strengths. The comparative dissolution data shows a very rapid drug release for both test and reference product i.e. more than 85% of the drug is dissolved within 15 minutes. The additional dissolution data support the full biowaiver for all strengths.

Manufacturing process
The product is 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 validated according to relevant European guidelines. Process validation data on the product have been presented for four blend batches of the minimum and maximum blend batch size and at least two batches of the filled capsules of each strength in accordance with the relevant European guidelines.

Control of excipients
All excipients are of Pharmacopoeial grade (Ph.Eur., USP, or USP/NF) and/or 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 (content uniformity), 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. 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 and for two batches of the 5 mg, 15 mg and 20 mg test products stored at

25°C/60% RH (12 months) and 40°C/75% RH (6 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 provided data the proposed shelf life of 24 months with storage condition "Store in the original package. This medicinal product does not require any special temperature storage conditions." can be granted.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
TSE/BSE certification has been provided for lactose anhydrous and CEP's for gelatine.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Lenalidomide Devatis 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 Lenalidomide Devatis is 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

This product is a generic formulation of Revlimid which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. 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.

IV.2 Pharmacokinetics

Biowaiver

The MAH did not submit clinical studies but performed a Biopharmaceutics Classification System (BCS) based biowaiver request for Lenalidomide hard capsules. According to the product specific guidance for lenalidomide, lenalidomide is a compound with complete absorption but the available data on solubility does not allow its BCS classification. If the MAH generates the solubility data and classifies the drug according to the BCS criteria as highly soluble, lenalidomide could be classified as BCS class I drug and a BCS biowaiver could be applicable.

It is agreed that lenalidomide has nearly complete or complete absorption. This is in line with the product specific guideline of Lenalidomide.
The MAH performed the required solubility study and these data confirm that lenalidomide is highly soluble at all pH ranges analysed (1.2 to 6.8) at 37°C, as per BCS definition. The minimum volume of media required to solubilize the highest strength (25 mg) is less than 250 ml across all pH ranges (1.2 to 6.8).

The proposed lenalidomide drug product is shown to be a very rapidly dissolving drug product as drug release was more than 85% in 15 minutes for all dosages and innovator product.
A BCS-based biowaiver is applied for all strengths and comparative, multimedia dissolution profiles of the test- and reference product have been provided for all seven strengths. The comparative dissolution data shows a very rapid drug release for both test and reference product i.e. more than 85% of the drug is dissolved within 15 minutes. The dissolution data support the full biowaiver for all strengths.

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 Lenalidomide Devatis.

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

Important identified risks	• Teratogenicity • Serious infection due to neutropenia • Second primary malignancy (SPM) • Important identified risk related to indication/target population • Tumour flare reaction (MCL indication)
Important potential risks	• Cardiac failure • Cardia arrhythmias • Ischaemic heart disease (including myocardial

	infarction) • Off label use
Missing information	None

In line with the RMP of the innovator, questionnaires are needed to be in place for risk of "teratogenicity", "SPM", and "tumour flare reaction (MCL indication).

The additional pharmacovigilance activities to assess the effectiveness of the MAH's additional risk minimisation measures (i.e. HCP kit, patient brochure and the pregnancy prevention programme) will be agreed on with the concerned health authorities at the national authorisation level.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Revlimid. No new clinical studies were conducted. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Lenalidomide Devatis 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 is a well-known medicinal product with an established favourable efficacy and safety profile.

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 Lenalidomide Devatis with

the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 15 October 2020.

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