COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Lenalidomide Alkaloid-INT 5 mg, 10 mg, 15 mg and 25 mg, hard capsules

(lenalidomide)

NL/H/5318/001-007/MR

Date: 27 September 2021

This module reflects the scientific discussion for the approval of Lenalidomide Alkaloid-INT 5 mg, 10 mg, 15 mg and 25 mg, hard capsules. The procedure was finalised at 3 February 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
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 Alkaloid-INT 5 mg, 10 mg, 15 mg and 25 mg, hard capsules , from Alkaloid - INT d.o.o..

The product is indicated for:
Multiple myeloma (MM)

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

- Lenalidomide Alkaloid-INT 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)

- Lenalidomide Alkaloid-INT as monotherapy is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (see sections 4.4 and 5.1 of the SmPC).

Follicular lymphoma (FL)

- Lenalidomide Alkaloid-INT 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 mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Revlimid, which has been registered in the EEA by Bristol-Myers Squibb Pharma EEIG through a centralised procedure (EU/1/07/391). Revlimid hard capsules with the strengths 5 mg, 10 mg, 15 mg and 25 mg were authorised in 2007.

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

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 report in which potential similarity between Lenalidomide Alkaloid-INT 5 mg, 10 mg, 15 mg and 25 mg, hard capsules and the innovator Revlimid was discussed. At the start of the assessment, it appeared that there was no orphan protection nor market exclusivity for Revlimid on any of the four indications. The orphan protection (EU/3/03/177) for Revlimid for the treatment of multiple myeloma (MM) expired in June 2017. The 10-years market exclusivity for the therapeutic indications MDS and MCL ended on 12 December 2019 upon request of the MAH and the orphan designation of the indication follicular lymphoma (FL) was withdrawn upon request of the MAH on 5 December 2019. On the basis of the report, the MEB could agree that lenalidomide is not similar to any of the currently authorised orphan medicinal product indicated for three out of four indications: MM (Ninlaro (ixazomib citrate), Kyprolis (carfilzomib), Farydak (panobinostat), Imnovid (pomalidomide), Darzalex (daratumumab) and BlenRep (belantamab mafodotin)), MDS (Reblozyl (iuspatercept)) and FL (Gazyvaro (obinutuzumab), all based on regulatory precedents supporting the non-similarity of lenalidomide and those products. For the treatment of MCL, there was also a regulatory precedent being set supporting the non-similarity of the lenalidomide and the currently authorised Imbruvia (ibrutinib). However, there was no such regulatory precedent supporting the non-similarity of lenalidomide and Tecartus (autologous anti-CD19-transduced CD3+ cells). It appeared that there was an overlap for the treatment of MCL. Nevertheless, the molecular structures and mechanisms of action were not similar. Therefore, the MEB could agree that lenalidomide is not similar to any authorised orphan medicinal product indicated for the treatment of MCL as well.

In conclusion, the MEB agreed that Lenalidomide Alkaloid-INT is not similar to any authorised orphan medicinal product indicated for the treatment of the four indications MM, MDS, MCL and FL.

II. QUALITY ASPECTS

II.1 Introduction

Lenalidomide Alkaloid-INT are hard gelatine capsules. The seven strengths can be distinguished by the colours of the cap and body, the imprints, and the capsule size.

- The 2.5 mg capsule has an opaque white body and opaque green to light green cap, marked “L9NL” and “2.5”. Each capsule contains as active substance 2.5 mg of lenalidomide.
- The 5 mg capsule has an opaque white body and opaque white cap, marked “L9NL” and “5”. Each capsule contains as active substance 5 mg of lenalidomide.

- The 7.5 mg capsule has an opaque white body and opaque yellow cap, marked “L9NL” and “7.5”. Each capsule contains as active substance 7.5 mg of lenalidomide.
- The 10 mg capsule has an opaque yellow body and opaque green to light green cap, marked “L9NL” and “10”. Each capsule contains as active substance 10 mg of lenalidomide.
- The 15 mg capsule has an opaque white body and opaque blue to light blue cap, marked “L9NL” and “15”. Each capsule contains as active substance 15 mg of lenalidomide.
- The 20 mg capsule has an opaque blue to light blue body and opaque green to light green cap, marked “L9NL” and “20”. Each capsule contains as active substance 20 mg of lenalidomide.
- The 25 mg capsule has an opaque white body and opaque white cap, marked “L9NL” and “25”. Each capsule contains as active substance 25 mg of lenalidomide.

The capsules are packed in oPA/Al/PVC/Al blisters.

The excipients are:
Capsule contents of all strengths - lactose, microcrystalline cellulose (E 460), croscarmellose sodium (E 468) and magnesium stearate (E 470b)

Capsule shell
- *2.5 mg* - gelatine, titanium dioxide (E171), indigotin (E132) and yellow iron oxide (E172)
- *5 mg* - gelatine and titanium dioxide (E171)
- *7.5 mg* - gelatine, titanium dioxide (E171) and yellow iron oxide (E172)
- *10 mg* - gelatine, titanium dioxide (E171), indigotin (E132) and yellow iron oxide (E172)
- *15 mg* - gelatine, titanium dioxide (E171) and indigotin (E132)
- *20 mg* - gelatine, titanium dioxide (E171), indigotin (E132) and yellow iron oxide (E172)
- *25 mg* - gelatine and titanium dioxide (E171

Printing ink of all strengths - shellac (E904), propylene glycol (E1520), black iron oxide (E172) and potassium hydroxide (E525)

The seven capsule strengths are dose proportional.

II.2 Drug Substance

The active substance is lenalidomide, this substance is not described in the European or British Pharmacopoeia (Ph. Eur.). Lenalidomide is a white to off-white powder. It is a racemate. It is soluble in N,N-dimethylformamide, dimethylsulfoxide, buffered aqueous solutions and ethanol/water, and insoluble in methanol and acetone. Lenalidomide exhibits polymorphism and is not hygroscopic.

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 a two-step synthesis. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised.

Quality control of drug substance

The drug substance specification of the ASMF-holder has been established in house. Batch analytical data demonstrating compliance with this specification have been provided for three batches for the two production sites.

Stability of drug substance

Stability data on the active substance have been provided for three commercial scale batches per production site, stored at 25°C/60% RH (up to 36 months) and 40°C/75% RH (six months) in double LDPE bags in an aluminium bag, put in a HDPE container, in accordance with applicable European guidelines. The ASMF-holder demonstrated the stability of the active substance for 36 months, including the polymorphic form. Based on the data submitted, a retest period could be granted of 24 months. The drug substance has been shown to be photostable under ICH Q1B conditions.

II.3 Medicinal Products

Pharmaceutical development

The products are an established pharmaceutical form and their development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained.

The drug products were developed using a Quality by Design (QbD) approach, but no Development of Experiments (DoE) studies are presented and no design space is claimed. The presented Quality Target Product Profile (QTPP) is considered appropriate in view of the intended use of the products. Formulation and manufacturing process developments were guided by risk assessments and material attributes and process parameters with medium and high risks for drug product Critical Quality Attributes (CQA) were evaluated. Sufficient information has been provided on formulation and manufacturing process development.

The proposed routine dissolution testing method is suitable and the proposed acceptance criterion sufficiently reflects the dissolution profile of the biobatch of the test products. The discriminatory nature of the method has been shown.

A biowaiver has been requested for the lower product strengths. Therefore, comparative dissolution profiles of the test- and reference products have been provided for these

strengths. The comparative dissolution studies complementary to the bioequivalence study support bioequivalence. The batch size of the biobatch of the test products has been justified. The maximum batch size of future commercial batches has been limited to the batch size of the biobatch of the test products.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. It consists of dry mixing and encapsulation. The manufacturing process has been described sufficiently and successfully validated for three production scale batches of the 2.5 mg, 5 mg, 10 mg and the 25 mg strength, on two batches of the 15 mg strength, and on one batch of the 7.5 mg and 20 mg strength.

Control of excipients

All excipients are of pharmacopeial grade (Ph. Eur., United States Pharmacopeia (USP), or USP/National Formulary (NF)) and/or in accordance with Commission Regulation 231/2012. The specifications of the excipients are acceptable.

Quality control of drug products

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identification, assay, impurities, dissolution and uniformity of dosage units. The proposed release and shelf life specifications are identical. They are supported by the provided batch analysis and stability data. The drug product specification is acceptable. 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 of the process validation batches from the proposed production sites have been provided, demonstrating compliance with the release specification. Sufficient information has been provided on the characterisation of impurities as well as a risk assessment regarding elemental impurities in line with ICH Q3D. Also an updated risk evaluation on nitrosamines impurities has been provided by the MAH, demonstrating compliance with EMA/189634/2019 for nitrosamines without further need of a control measure.

Stability of drug product

Stability data on the product have been provided for the process validation batches stored at 25°C/60% RH (24 months) and 40°C/75% RH (six months). The studies were carried out using three production scale batches of the 2.5 mg, 5 mg, 10 mg, and the 25 mg strength, two production scale batches of the 15 mg strength, and on one production scale batch of the 7.5 mg and 20 mg strength. The batches were stored in oPA/Al/PVC – Al blisters. Except for appearance, no significant changes or trends were seen at both storage conditions. The colour spectrum resulting from potential fading of the green and blue capsules parts was considered as a cosmetic artifact and has been included in the description of the appearance of the capsules in the drug product specification and section 3 of the SmPC. The conditions used in the stability studies are in accordance with applicable European guidelines demonstrating the stability of the product for 24 months. The drug product was shown to be photostable under

ICH Q1B conditions. On basis of the data submitted, a shelf life was granted of 36 months. No specific storage conditions are needed.

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 for lactose and gelatine. Magnesium stearate is of vegetable origin.

II.4 Discussion on chemical, pharmaceutical and biological aspects

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

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Lenalidomide Alkaloid-INT 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 products are 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.

For this generic application, the MAH has submitted one bioequivalence study for the 25 mg capsule, which is discussed below. A biowaiver is applied for the lower strengths 2.5, 5, 7.5, 10, 15 and 20 mg capsules.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Lenalidomide Alkaloid-INT 25 mg, hard capsules (Alkaloid - INT d.o.o., Slovenia) is compared with the pharmacokinetic profile of the reference product Revlimid 25 mg hard capsules (Bristol-Myers Squibb Pharma EEIG, Ireland).

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

Biowaiver

The MAH applied for a biowaiver for the lower strengths 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg capsules. All the different strengths are manufactured by the same manufacturing process. All strengths of the test product had the same qualitative composition and were quantitatively dose-proportional. The pharmacokinetics of lenalidomide was linear across the therapeutic dose range. Comparative dissolution similarity was demonstrated as dissolution at the 3 relevant pHs was more than 85% in 15 minutes in all media.
Overall, the criteria for a biowaiver based on the current Guideline on the Investigation of Bioequivalence were met and a waiver was granted.

Bioequivalence study

Design

A single-dose, open label, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 26 healthy male subjects, aged 22-51 years. Each subject received a single dose (25 mg) of one of the two lenalidomide formulations. The tablet was orally administered with 200 ml water after an overnight fast of 10.5 hours. There were two dosing periods, separated by a washout period of seven days.

Blood samples were collected at pre-dose and at 0.17, 0.33, 0.5, 0.67, 0.83, 1, 1.25, 1.5, 1.75, 2, 2.33, 2.67, 3, 3.5, 4, 5, 6, 8, 10, 12, 16 and 24 hours after administration of the products.

The design of the study is acceptable. Lenalidomide may be taken without reference to food intake. Lenalidomide is rapidly absorbed following oral administration in healthy volunteers, under fasting conditions, with maximum plasma concentrations occurring between 0.5 and 2 hours post-dose. In patients, as well as in healthy volunteers, the maximum concentration (C_{max}) and area-under-the-concentration time curve (AUC) increase proportionally with increases in dose. Multiple dosing did not cause marked medicinal product accumulation.
Co-administration with a high-fat and high-calorie meal in healthy volunteers reduces the extent of absorption. However, in the main multiple myeloma (MM) and myelodysplastic

syndromes (MDS) registration trials where the efficacy and safety were established for lenalidomide, the medicinal product was administered without regard to food intake. Thus, lenalidomide can be administered with or without food. Population pharmacokinetic analyses indicate that the oral absorption rate of lenalidomide is similar among MM, MDS and MCL patients. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

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

Results
All 26 subjects completed the study and were eligible for pharmacokinetic analysis.

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

Treatment N=26	**AUC_{0-24} (ng/ml/h)**	**$AUC_{0-\infty}$ (ng/ml/h)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	1339.8 ± 232	1358.7 ± 229	418.2 ± 115	0.83 (0.50 – 2.00)
Reference	1360.2 ± 15781	1379.6 ± 248	417.2 ± 131	0.67 (0.50 – 2.33)
***Ratio (90% CI)**	0.99 (0.96 – 1.01)	0.99 (0.96 – 1.01)	1.01 (0.95 – 1.08)	-

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration

**ln-transformed values*

Conclusion on bioequivalence study
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Lenalidomide Alkaloid-INT 25 mg, hard capsules are considered bioequivalent with Revlimid 25 mg hard capsules.

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

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Lenalidomide Alkaloid-INT.

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

Important identified risks	- Second primary malignancies - Serious infection due to neutropenia - Teratogenicity <u>Important identified risks related to indication/target population</u> - For mantle cell lymphoma and follicular lymphoma: Tumour flare reaction
Important potential risks	- Cardiac arrhythmias - Cardiac failure - Ischaemic heart disease (including myocardial infarction) - Off label use
Missing information	None

Next to routine pharmacovigilance activities and routine risk minimisation measures, the MAH committed to perform additional risk minimisation measures pursuant to Article 21a/22 of Directive 2001/83/EC. In line with the RMP of the innovator, specific targeted follow-up questionnaires will be implemented for risk of cardiac failure and cardiac arrhythmias, ischaemic heart disease (including myocardial infarction), second primary malignancies, serious infection due to neutropenia and teratogenicity. The MAH will also provide additional risk minimisation measures in the form of educational material (for prescribers and patients, as well as patient card) for the risk of teratogenicity. It is agreed that implementation of the additional risk minimisation measures and the details of the controlled distribution system will be agreed with the competent authority of each individual member state in the EU.

The risk management plan was considered acceptable.

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. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

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 Revlimid 5 mg, 10 mg, 15 mg and 25 mg hard capsules (EMEA/H/C/000717). 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

Lenalidomide Alkaloid-INT 5 mg, 10 mg, 15 mg and 25 mg, hard capsules have a proven chemical-pharmaceutical quality and are generic forms of Revlimid 5 mg, 10 mg, 15 mg and 25 mg hard capsules. Revlimid is a well-known medicinal product with an established favourable efficacy and safety profile.

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

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 Alkaloid-INT with the reference product, and have therefore granted a marketing authorisation. This mutual recognition procedure was finalised with a positive outcome on 3 February 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