COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

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

(lenalidomide)

NL/H/4286/001-007/DC

Date: 16 January 2020

This module reflects the scientific discussion for the approval of Lenalidomide Grindeks. The procedure was finalised on 21 August 2019. 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
HCP	Healthcare Professional
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
SPM	Second Primary Malignancies
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 Grindeks 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg and 25 mg hard capsules from AS Grindeks.

Lenalidomide Grindeks is indicated for:

Multiple myeloma (MM)

- as monotherapy for the maintenance treatment of adult patients with newly diagnosed multiple myeloma (MM) who have undergone autologous stem cell transplantation.
- as combination therapy (see SmPC section 4.2) for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant.
- in combination with dexamethasone for the treatment of multiple myeloma in adult patients who have received at least one prior therapy.

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

The following indications which are covered by orphan designation for the product Revlimid, were not applied for:

- Myelodysplastic syndromes (MDS)
- Mantle cell lymphoma (MCL)

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Revlimid hard capsules (EU/1/07/391), which has been registered in the EEA via a centralised procedure by Celgene Europe Ltd since 14 June 2007.

The concerned member states (CMS) involved in this procedure were Bulgaria, Croatia, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Romania, Slovakia 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 assessment report versus the following orphan medicinal products:

- Ninlaro (ixazomib)
- Kyprolis (carfilzomib)
- Farydak (panobinostat)
- Darzalex (daratumumab)
- Imnovid (pomalidomide)

Ixazomib, carfilzomib, daratumumab and panobinostat neither belong to the same pharmacotherapeutic group nor show any similarity in active substance compared to lenalidomide. Having considered the arguments presented by the MAH, it can be concluded that lenalidomide and pomalidomide are not similar because of a difference in therapeutic indication. Lenalidomide Grindeks is non-similar (as defined in Article 3 of Commission Regulation (EC) No 847/2000) to any of the products listed above.

II. QUALITY ASPECTS

II.1 Introduction

Lenalidomide Grindeks 2.5 mg is a light-green/white capsule, marked “L2.5” with white or almost white powder.
Lenalidomide Grindeks 5 mg is a white capsule, marked “L5” with white or almost white powder.
Lenalidomide Grindeks 7.5 mg is a pale yellow/white capsule, marked “L7.5” with white or almost white powder.
Lenalidomide Grindeks 10 mg is a light-green/pale yellow capsule, marked “L10” with white or almost white powder.
Lenalidomide Grindeks 15 mg is a blue/white capsule, marked “L15” with white or almost white powder.
Lenalidomide Grindeks 20 mg is a light-green/blue capsule, marked “L20” with white or almost white powder.
Lenalidomide Grindeks 25 mg is a white capsule, marked “L25” with white or almost white powder.

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 (as lenalidomide ammonium chloride).

The hard capsules are packed in Al/PVC/Aclar/PVC blisters.

The excipients of the capsule fill are microcrystalline cellulose, lactose, croscarmellose sodium and magnesium stearate. Excipients of the capsules are gelatin and colourants (titanium dioxide, yellow iron oxide, and brilliant blue FCF – FC&C Blue I).
Excipients of the printing ink are shellac, propylene glycol, black iron oxide, potassium hydroxide and concentrated ammonia solution.

The seven strengths are fully dose proportional with regards to their capsule contents.

II.2 Drug Substance

The drug substance is lenalidomide, an established active substance, which is not described in the European Pharmacopoeia (Ph.Eur.), British Pharmacopoeia (BP) or United States Pharmacopoeia (USP). The active substance is a white or almost white to pale yellow powder, which is very slightly soluble in water. Lenalidomide is used in the form of a cocrystal with ammonium chloride as co-former. Lenalidomide ammonium chloride cocrystal exists in a single polymorphic form. The active substance incorporates one stereogenic centre in its structure and is a racemate. The drug substance is micronised.

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 active substance is manufactured in a two step synthesis. The selection of the starting materials has been sufficiently justified. The specifications for the proposed starting materials are acceptable. No class 1 solvents are used. No heavy metal catalysts are used. The specifications for the solvents, reagent and catalyst are acceptable. The active substance has been sufficiently 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, with an additional requirement for particle size distribution. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided three full-scale batches.

Stability of drug substance

Stability data on the active substance have been provided for three full-scale batches of the micronized drug substance and non-micronized drug substance, stored at 25°C/60% RH (18 months) and 40°C/75% RH (6 months). No changes in loss on drying, ammonium chloride content, assay, related substances and microbiological quality are observed at long-term and accelerated conditions. Photostability is demonstrated. A retest period of 24 months without any storage restrictions has been granted.

II.3 Medicinal Product

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies performed concerned amongst others the characterisation of the reference product, optimization of the formulation and dissolution method development. The discriminatory nature of the dissolution method has been adequately shown. The choices of the packaging and manufacturing process are justified. The seven strengths can be visually distinguished by the colours of the cap and body, the imprints and the capsule size.

Bioequivalence studies have been performed with the 25 mg strength and 15 mg strength. Both biobatches were manufactured according to the finalized composition and manufacturing process. The dissolution studies in support of the biowaiver of additional strengths were carried out in 0.1M HCl pH 1.2, acetate buffer pH 4.5, and phosphate buffer pH 6.8 using the basket apparatus at 100 rpm. Similarity is demonstrated for all strengths versus the biobatches in the three media/pHs.

Manufacturing process

The manufacturing process consists of dry mixing and encapsulation. The description of the manufacturing process is considered acceptable. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for two full-scale and two pilot-scale batches of common blend that were used to prepare four batches of the 2.5 mg and 25 mg products (pilot and full-scale) and one or two pilot-scale batches of each of the intermediate strengths using a bracketing approach. The product is manufactured using conventional manufacturing techniques. Therefore process validation for full-scale batches up to a total of three batches per strength can be performed post authorisation.

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 product specification includes tests for description, identification, average mass of capsule content, uniformity of dosage units (content uniformity), disintegration time, water content, dissolution, assay, related substances and microbiological quality. The release and shelf-life specifications differ with regards to the methods for identification, limit for water content and limits for related substances. The drug product specification is acceptable.

Analytical methods were adequately described and validated. The batch analysis data of eleven batches demonstrate compliance with the release specification.

A risk assessment regarding elemental impurities, in line with ICH Q3D, has been provided.

Stability of drug product

Stability data on the product has been provided for three batches of the extreme strengths and one batch of each of the intermediate strengths, stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the commercial packaging. No significant changes were observed during the stability studies and the data may be extrapolated. Photostability has been demonstrated under ICH Q1B conditions. The proposed shelf-life of 36 months has been granted with the storage condition 'This medicinal product does not require any special storage conditions'.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Gelatin, used for the capsules, and the excipient lactose anhydrous are of animal origin. TSE/BSE-statements have been provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Lenalidomide Grindeks 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 Grindeks 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.

For this generic application, the MAH has submitted two bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

Bioequivalence studies

The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the Lenalidomide Grindeks 15 mg and 25 mg hard capsules (AS Grindeks, Latvia) is compared with the pharmacokinetic profile of the Revlimid 15 mg and 25 mg hard capsules (Celgene Europe Ltd, the Netherlands).

The choice of the reference product in the bioequivalence study is justified, as it has been authorised through a centralised procedure. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Both bioequivalence studies were conducted under fasting conditions, which is acceptable as the product can either be taken with or without food.

Analytical/statistical methods

The analytical methods have been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in the bioequivalence studies for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Biowaiver

A biowaiver for the additional strengths of 2.5, 5, 7.5 and 10 mg has been granted based on the bioequivalence study with the 15 mg strength. A biowaiver for the 20 mg strength has been granted based on the bioequivalence study with 25 mg strength. The following prerequisites are met:

- The strengths have been manufactured by the same manufacturing process
- The qualitative composition of the strengths is the same and the composition of the strengths is quantitatively proportional.
- The pharmacokinetics of lenalidomide can be considered dose linear within the dose range up to 35 mg.

- In accordance to the requirements given in the relevant guidance Guideline on the investigation of Bioequivalence an appropriate dissolution study covering the desired pH range has been performed.

Bioequivalence study I: 25 mg strength

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 28 healthy male subjects, aged 19-48 years. Each subject received a single dose (25 mg) of one of the 2 lenalidomide formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. There were 2 dosing periods, separated by a washout period of at least 3 days.

Blood samples were collected pre-dose and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 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. The wash-out period of 3 days is sufficient since the half-life of lenalidomide is approximately 3 hours. The sampling period and sampling times are adequate based on the fact that C_{max} is expected after 0.5-2 h after the administration.

Results

Twenty-eight subjects were dosed in period I. Two subjects were withdrawn in period I: one subjects was withdrawn due to the detection of alcohol in the blood during the admission screening to period II, and another subject discontinued the study due to his own will before period II. The remaining 26 subjects were dosed in period II, completed the crossover and were included in the bioequivalence assessment.

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

Treatment N=26	**AUC_{0-t}** (ng.h/ml)	**$AUC_{0-\infty}$** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)	**$t_{1/2}$** (h)
Test	1355.4 ± 170.63	1361.7 ± 185.10	466.506 ± 83.86	0.67 (0.67 - 1.33)	--
Reference	1366.3 ± 169.60	1373.2 ± 184.50	470.088 ± 125.95	0.67 (0.67 - 1.67)	--
***Ratio (90% CI)**	1.00 (0.98-1.02)	--	1.01 (0.92 – 1.12)	--	--
CV (%)	4.59	--	20.61	--	--

$AUC_{0-\infty}$ 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
$t_{1/2}$ half-life
CV coefficient of variation

**ln-transformed values*

Bioequivalence study II: 15 mg strength

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 28 healthy male subjects, aged 18-40 years. Each subject received a single dose (15 mg) of one of the 2 lenalidomide formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. There were 2 dosing periods, separated by a washout period of 5 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.33, 1.67,2,2.5,3,3.5, 4, 6, 8, 10, 12, 16 and 24 hours after administration of the products.

The design of the study is acceptable. The wash-out period of 5 days is sufficient since the half-life of lenalidomide is approximately 3 hours. The sampling period and sampling times are adequate based on the fact that C_{max} is expected after 0.5-2 h after the administration.

Results

All 28 subjects were dosed in period I and in period II and were eligible for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of lenalidomide under fasted conditions

Treatment N=28	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Test	917.31 ± 146.37	--	311.868 ± 75.45	0.75 (0.50 – 1.67)	--
Reference	939.63 ± 169.58	--	313.929 ± 64.16	0.75 (0.50 – 3.00)	--
***Ratio (90% CI)**	0.98 (0.95-1.01)	--	0.99 (0.92-1.06)	--	--
CV (%)	5.68	--	16.18	--	--

$AUC_{0-\infty}$	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
$t_{1/2}$	half-life
CV	coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence studies

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80-1.25. Based on the submitted bioequivalence studies Lenalidomide Grindeks 15 mg and 25 mg are considered bioequivalent with Revlimid 15 mg and 25 mg.

The MEB has been assured that the bioequivalence studies have 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 Grindeks.

Table 3. Summary table of safety concerns as approved in RMP

Important identified risks	• Teratogenicity • Serious infection due to neutropenia • Second Primary Malignancies
Important potential risks	• Cardiac failure • Cardiac arrhythmias • Ischaemic heart disease (including myocardial infarction) • Off-label use
Missing information	• None

In line with the reference product questionnaires are place for the risk of “teratogenicity”, “cardiac failure and cardiac arrhythmias” and “ischemic heart disease (including myocardial infarction)”.

In line with the reference product additional risk minimization measures are linked to the risks of “teratogenicity” and “secondary primary malignancies”. The key elements of the additional risk minimization measures are in line with the reference product and therefore accepted

The additional risk minimisations measures should be in place as following:

- Teratogenicity:
  Pregnancy Prevention Programme, Healthcare Professional (HCP) KIT, patient brochure, checklists, patient card
- Thrombocytopenia and bleeding
  HCP brochure, Patient brochure
- Neutropenia and infection
  HCP brochure, patient brochure
- Thromboembolic events

HCP brochure, patient brochure
- Cutaneous reaction
  HCP brochure
- Hypersensitivity and angioedema
  HCP brochure
- Acute myeloid leukaemia and B-cell malignancies
  HCP brochure
- Tumour Flare Reaction
  HCP kit
- Peripheral neuropathy
  HCP brochure
- Renal failure
  HCP brochure
- Hepatic disorders
  HCP brochure
- Other SPM
  HCP brochure
- Use in moderate and severe hepatic impairment
  HCP brochure

The educational Health Care Professional's kit should consist of the following:
- HCP brochure
- Check list for physicians
- Adverse event reporting forms

The educational brochures for patients should consist of the following:
- Brochure for female patients of childbearing potential and their partners
- Brochure for female patients who are not of childbearing potential
- Brochure for male patients
- Patient card

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

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 overall observational conclusion reached by the interviewers was that the PIL is well structured and organised, easy to understand and written in a comprehensible manner, and that the test shows that the leaflet is readable and patients/users are able to act upon the information that it contains. No changes were made to the PL during the user testing process. General comments on the format and layout of the leaflet were positive. The font of the headings and subheadings was increased after the testing.
Overall 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 Grindeks 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 25 mg, hard capsules has a proven chemical-pharmaceutical quality and is a generic form of Revlimid 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 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 Grindeks with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 21 August 2019.

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