COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

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

(lenalidomide hydrochloride hydrate)

NL/H/4067/001-007/DC

Date: 28 February 2019

This module reflects the scientific discussion for the approval of Lenalidomide ratiopharm. The procedure was finalised at 12 July 2018. 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
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 ratiopharm 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 25 mg, hard capsules from Ratiopharm GmbH.

Lenalidomide ratiopharm is indicated for:

Multiple myeloma (MM)

- as monotherapy for the maintenance treatment of adult patients with newly diagnosed multiple myeloma 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.

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

Myelodysplastic syndromes (MDS)
Revlimid 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)
Revlimid as monotherapy is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma.

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 Ltd 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:

Table 1. Medical products

Tradename (act. subst.)	Orphan design. nr	Date
Ninlaro (ixazomib)	EU/3/11/899	23/11/2016
Kyprolis (carfilzomib)	EU/3/08/548	23/11/2015
Farydak (panobinostat)	EU/3/12/1063	01/09/2015
Imnovid (pomalidomide)	EU/3/09/672	08/08/2013
Thalidomide Celgene	EU/3/01/067	18/04/2008
Darzalex (daratumumab)	EU/3/13/1153	24/05/2016

It is concluded that, having considered the arguments presented by the MAH of lenalidomide, the indication and mechanism of action of lenalidomide and the other active substances are not similar in the context of orphan medicinal products. Lenalidomide ratiopharm 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 ratiopharm is a hard non-transparent capsule in seven strengths containing off-white to pale yellow or beige powder or compressed powder:

- 2.5 mg hard capsules are imprinted in black with ‘2.5’ on a white body and with a green cap.
- 5 mg hard capsules are imprinted in black with ‘5’ on a white body and with a white cap.
- 7.5 mg hard capsules are imprinted in black with ‘7.5’ on a white body and with an ivory cap.
- 10 mg hard capsules are imprinted in black with ‘10’ on an ivory body and with a green cap.
- 15 mg hard capsules are imprinted in black with ‘15’ on a white body and with a blue cap.
- 20 mg hard capsules are imprinted in black with ‘20’ on a blue body and with a green cap.
- 25 mg hard capsules are imprinted in black with ‘25’ on a white body and with a white cap.

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 capsules are packed in OPA/Al/PVC-Al blisters.

The excipients are:
Capsule contents
- Silica, colloidal anhydrous
- Cellulose, microcrystalline
- Croscarmellose sodium
- Talc

Capsule shell
2.5 mg, 10 mg and 20 mg strengths:
- Gelatin
- Titanium dioxide (E171)
- Yellow iron oxide (E172)
- Indigo carmine (E132)

5 mg and 25 mg strengths:
- Gelatin
- Titanium dioxide (E171)

7.5 mg strength:
- Gelatin
- Titanium dioxide (E171)
- Yellow iron oxide (E172)

15 mg strength:
- Gelatin
- Titanium dioxide (E171)
- Indigo carmine (E132)

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

The 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, and 25 mg capsule strengths are dose proportional. The 2.5 mg strength is weight proportional to the 5 mg strength

II.2 Drug Substance

The active substance is lenalidomide hydrochloride hydrate, an established active substance that is not described in the European Pharmacopoeia (Ph.Eur.). Lenalidomide hydrochloride

hydrate is a white or almost white crystalline powder. The drug substance is highly soluble. It exhibits polymorphism. The stability of the used polymorphic form has been demonstrated.

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 is sufficiently described. The synthesis has adequately been described. The starting materials of the synthesis are acceptable. Potential carry-over and control of impurities from the synthesis has adequately been discussed and is acceptable.

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 five batches.

Stability of drug substance

Stability data on the active substance have been provided for three batches stored at 25°C/60% RH (18 months data), at 30°C/65% RH (12 months data) and at 40°C/75% RH (6 months data). Based on the data submitted, a retest period could be granted of 30 months without special storage conditions.

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 development of the drug product is based on the reference product Revlimid, but different excipients are used. The choice of excipients is justified and their functions explained.

Bioequivalence studies have been carried out with 2.5 mg and 25 mg strengths. The batch size and potency of the products used are acceptable. The data show that more than 85% is dissolved in 15 minutes, indicating comparable dissolution profiles with the reference product. Information on particle size distribution of the drug substance batches used to manufacture the biobatches has been provided and it supports the proposed limit for the particle size distribution in the drug substance specification. The biowaiver for the 5 mg and 7.5 mg, 10 mg, 15 mg and 25 mg strengths is supported by the comparable dissolution profiles.

Manufacturing process

The drug product is prepared by a standard manufacturing process and comprises two major steps: screening and blending, and encapsulation. No process validation data are provided, but during development, stability batches for all strengths (three batches for 2.5 mg and 25 mg each and two batches for the other strengths each) have been evaluated for relevant quality parameters screening/blending and encapsulation steps in the manufacturing process, demonstrating similarity of the produced batches.

Control of excipients

The excipients used are commonly used for this type of drug product and comply with Ph. Eur. These specifications 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 of the drug product and capsule content, identification of lenalidomide, water content, content uniformity, assay, impurities, dissolution and microbiological examination. 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 sufficient batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability studies at accelerated (6 months), and long-term conditions (18 months) have been provided for two batches per strength (three batches for 2.5 mg and 25 mg). All stability data comply with the originally proposed specification. The product is found to be photostable. On basis of the data submitted, a shelf life was granted of 2 years without special storage conditions.

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

Gelatin is the only material of animal or human origin included in the drug product. 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 Lenalidomide ratiopharm 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 ratiopharm 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 hydrochloride hydrate 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 ratiopharm 2.5 mg and 25 mg, hard capsules (Ratiopharm GmbH, Germany) is compared with the pharmacokinetic profile of the Revlimid 2.5 mg and 25 mg hard capsules (Celgene Europe Ltd, Germany).

The choice of the reference product in the bioequivalence study is been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

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.

Biowaiver
For Lenalidomide ratiopharm, all products were manufactured by the same process and the composition of the different strengths is qualitatively the same. The composition of the strengths (i.e. 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg and 25 mg) is dose proportional.

The dissolution data of Lenalidomide ratiopharm 5 mg to 25 mg capsules were presented in the quality assessment report. At pH 1.2, 4.5 and 6.8, capsules from all six strengths dissolved more than 85% within 15 minutes. Therefore, similarity in dissolution has been demonstrated at the three requested pH levels between the lower strengths (5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg) and the 25 mg strength of Lenalidomide ratiopharm.

Therefore, the conclusion of the bioequivalence study with the lenalidomide 25 mg strength can be extrapolated to the lower strengths of 5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg capsules.

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 26 healthy male subjects (41 ± 11 years). Each subject received a single dose (25 mg) of one of the two lenalidomide formulations. The tablet was orally administered with 240 ml water. There were two dosing periods, separated by a washout period of six days.

Blood samples were collected pre-dose and at 0.167, 0.25, 0.333, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, 10, 12 and 15 hours after administration of the products.

The design of the study is acceptable. The wash-out period of 6 days is considered to be adequate to avoid any carry-over. Pre-dose levels were not observed in any subject. The sampling scheme is considered appropriate.

Results
23 Subjects were eligible for pharmacokinetic analysis. The reasons for withdrawal of three subjects are acceptable.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of 25 mg lenalidomide under fasted conditions.

Treatment N=23	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	1599.8 ± 350	1657.5 ± 374	476.7 ± 121	0.75 (0.5 - 1.75)
Reference	1580.3 ± 331	1636.8 ± 352	440.6 ± 120	0.75 (0.33 - 2.0)
***Ratio (90% CI)**	1.0 (0.98 - 1.03)	--	1.08 (1.0 - 1.17)	--
CV (%)	5	--	15	--

$AUC_{0-\infty}$ 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: 2.5 mg strength

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 26 healthy male subjects (36 ± 10 years). Each subject received a single dose (2.5 mg) of one of the two lenalidomide formulations. The tablet was orally administered with 240 ml water. There were two dosing periods, separated by a washout period of six days.

Blood samples were collected pre-dose and at 0.25, 0.333, 0.5, 0.67, 0.83, 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12 and 15 hours after administration of the products.

The design of the study is acceptable. The wash-out period of six days is considered to be adequate to avoid any carry-over. Pre-dose levels were not observed in any subject. The sampling scheme is considered appropriate.

Results

23 Subjects were eligible for pharmacokinetic analysis. The reasons for withdrawal of three subjects are acceptable.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of 2.5 mg lenalidomide under fasted conditions.

Treatment N=23	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	147.9 ± 16.8	153.1 ± 18	49.0 ± 11	0.67 (0.5 - 1.25)
Reference	145.4 ± 17.1	151 ± 18.5	47.0 ± 12	0.67 (0.5 - 2.0)
***Ratio (90% CI)**	1.01 (0.98 - 1.04)	--	1.03 (0.97 - 1.09)	--
CV (%)	5	--	11	--

$AUC_{0-\infty}$ 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 ratiopharm is considered bioequivalent with Revlimid.

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 ratiopharm.

Table 4. 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	--

Additional risk minimisation measures for physicians and patients are deemed necessary for two safety concerns.

Teratogenicity
- Pregnancy Prevention Programme (PPP)
- Educational healthcare professional's kit, consisting of healthcare professional brochure and check list for physicians
- Educational brochures for patients consisting 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
- Controlled distribution system (CDS)

Second Primary Malignancies
- Educational material for physicians

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 product the risk minimisation materials should be part of the conditions to the marketing authorisation.

Routine risk minimisation activities for all other safety concerns are considered sufficient for this product.

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 results

show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and PL of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Lenalidomide ratiopharm 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 ratiopharm with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 12 July 2018.

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