COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

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

(lenalidomide)

NL/H/4084/001-007/DC

Date: 14 February 2019

This module reflects the scientific discussion for the approval of Lenalidomide Synthon. The procedure was finalised at 8 August 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 Synthon 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 25 mg, hard capsules from Synthon BV.

Lenalidomide Synthon 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 Malta.

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 Synthon 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 Synthon is a hard capsule:
2.5 mg - Opaque white body and opaque green to light green cap, marked “L9NL” and “2.5”
5 mg - Opaque white body and opaque white cap, marked “L9NL” and “5”
7.5 mg - Opaque white body and opaque yellow cap, marked “L9NL” and “7.5”
10 mg - Opaque yellow body and opaque green to light green cap, marked “L9NL” and “10”
15 mg - Opaque white body and opaque blue to light blue cap, marked “L9NL” and “15”
20 mg - Opaque blue to light blue body and opaque green to light green cap, marked “L9NL” and “20”
25 mg - Opaque white body and opaque white cap, marked “L9NL” and “25”

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
- Cellulose, microcrystalline (E460 (i))
- Croscarmellose sodium (E468)

- Magnesium stearate (E470b)

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 (E904)
- Propylene glycol (E1520)
- Black iron oxide (E172)
- Potassium hydroxide (E525)

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 well soluble in terms of the BCS classification system across the physiological pH range with highest solubility at low pH. The active substance is present as a racemate. The manufacturing process yields polymorphic form A.

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 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 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 three batches of both active substance manufacturers.

Stability of drug substance

Stability data on the active substance have been provided for three commercial scale batches of both active substance manufacturers stored at 25°C/60% RH (manufacturer-I: 24 months, manufacturer-II: 36 months) and 40°C/75% RH (six months). It has been demonstrated for batches stored up to 36 months that the polymorphic form does not change. Based on the data submitted, a retest period could be granted of 24 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 drug product was developed using a quality by design approach. The presented quality target product profile (QTPP) is considered appropriate in view of the intended use of the product. Formulation and manufacturing process developments were guided by risk assessments. 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 comparative dissolution studies complementary to the bioequivalence study support bioequivalence. The batch size of the biobatch of the test product has been justified with the small market due to the orphan designation. The maximum batch size of future commercial batches has been limited to the batch size of the biobatch of the test product.
The proposed routine dissolution testing method is suitable and the proposed acceptance criterion sufficiently reflects the dissolution profile of the biobatch of the test product. The discriminatory nature of the method has been shown.

The dissolution studies in support of the biowaiver for the lower strengths were carried out in simulated gastric fluid (SGF) pH 1.2, acetate buffer pH 4.5, and phosphate buffer pH 6.8. More than 85% was dissolved in 15 minutes in all media.

Manufacturing process

The manufacturing process consists of dry mixing and encapsulation. It is regarded as a standard process. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented 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 in accordance with the relevant European guidelines.

Control of excipients

All excipients are of pharmacopoeial grade (Ph.Eur., United States Pharmacopoeia (USP), or USP/National Formulary (NF)) and/or in accordance with Commission Regulation 231/2012. 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 appearance, identification, assay, impurities, dissolution, and uniformity of dosage units. 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 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 from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product has been provided for the process validation batches stored at 25°C/60% RH (24 months) and 40°C/75% RH (six months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed packaging. The proposed shelf life of 36 months can be granted. No specific storage restrictions are considered necessary. The drug product was shown to be photostable under ICH Q1B conditions.

Except for appearance, no significant changes or trends were seen at both storage conditions. The colour of the capsule parts containing indigotine faded in some batches stored at accelerated conditions. It is agreed with the MAH that this discolouration can be considered a cosmetic artifact which is likely to occur in the reference product as well. The colour spectrum resulting from potential fading of green and blue capsules parts has been included in the description of the appearance of the capsules in the drug product specification and section 3 of the SmPC.

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 Lenalidomide Synthon 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 Synthon 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 one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Lenalidomide Synthon 25 mg hard capsules (Synthon BV, The Netherlands) is compared with the pharmacokinetic profile of the reference product Revlimid 25 mg hard capsules (Celgene Europe Limited).

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

Biowaiver

A waiver for the additional strengths 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg is being applied for based on the following:

- All the different strengths are manufactured by the same manufacturing process.
- The qualitative composition of the capsule content is the same and quantitatively proportional for the various strengths.
- *In vitro* dissolution data confirm similarity between the claimed strengths. Dissolution at the three relevant pHs was more than 85% in 15 minutes.
- The pharmacokinetics of lenalidomide are linear over the dose range 5 mg to 400 mg.

Overall, the criteria for a biowaiver based on the current Guideline on the Investigation of Bioequivalence are met and a waiver is granted.

Bioequivalence study

Design

An open label, randomised, two-sequence, two-treatment, two period, single dose, cross-over 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 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.

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 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-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	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 – 1.09)	--

$AUC_{0-\infty}$ 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 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 Synthon 25 mg is considered bioequivalent with Revlimid 25 mg.

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 Synthon.

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

Important identified risks	• Second primary malignancies • Serious infection due to neutropenia • Teratogenicity
Important potential risks	• Cardiac arrhythmias • Cardiac failure • 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

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. 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 Synthon 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 Synthon with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 8 August 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