COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Lenalidomide Reddy 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg and 25 mg hard capsules (lenalidomide)

NL/H/5528/001-007/DC

Date: 6 February 2024

This module reflects the scientific discussion for the approval of Lenalidomide Reddy 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg and 25 mg hard capsules. The procedure was finalised on 27 April 2023. 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
BCS	Biopharmaceutical Classification System
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
EMA	European Medicines Agency
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
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Reference Member State has granted a marketing authorisation for Lenalidomide Reddy 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg and 25 mg hard capsules, from Reddy Holding GmbH.

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

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

Lenalidomide Reddy 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
Lenalidomide Reddy 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
Lenalidomide Reddy as monotherapy is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma.

Follicular lymphoma
Lenalidomide Reddy 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 up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this decentralised procedure, essential similarity is proven between the new product and the innovator product Revlimid 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg and 25 mg hard capsules, which have been registered in the EEA by Bristol-Myers Squibb Pharma EEIG via a centralised procedure (EU/1/07/391/001-014) since 14 June 2007.

The concerned member state (CMS) involved in this procedure was Romania (5 mg, 10 mg, 15 mg and 25 mg only).

Similarity assessment

According to Article 8(1) of Regulation (EC) No 141/2000, no marketing authorisation can be granted for a product similar to an orphan medicinal product for a period of ten years, when this concerns a similar medicinal product with the same therapeutic indication. Based on the analysis conducted on chemical structure, indication and mechanism of action, it can be concluded that lenalidomide is not similar with other orphan medicinal product for which a marketing authorisation in the EU has been granted, for a condition relating to the indications proposed in this application.

As a conclusion, Lenalidomide 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg and 25 mg capsules cannot be considered a similar medicinal product to Ninlaro (Ixazomib), Abecma, Kyprolis (Carfilzomib), Darzalex (Daratumumab), Blenrep (belantamab mafodotin), Panobinostat, Pomalidomide, Carvykti (ciltacabtagene autoleucel) in multiple myeloma, Gazyvaro (Obinutuzumab), Yescarta, Lunsumio, Kymriah in follicular lymphoma, Reblozyl in myelodysplastic syndromes and Tecartus in mantle cell lymphoma for the purpose of Regulations (EC) No 141/2000 and 847/2000.

II. QUALITY ASPECTS

II.1 Introduction

Lenalidomide Reddy is a hard capsule. Lenalidomide Reddy 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg and 25 mg hard capsules contain 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg and 25 mg of lenalidomide. All capsule strengths are dose proportional, except for the 2.5 mg strength. The different strengths can be distinguished by the colour and size of the capsule, and the printed text on the capsules.

Lenalidomide Reddy 2.5 mg hard capsules contain white to yellow coloured powder. The hard capsule has a grey body and grey cap, size 4 (approx. 14.3 mm), marked “LEU” on the cap and “2.5” on the body with black ink.

Lenalidomide Reddy 5 mg hard capsules contain white to yellow coloured powder. The hard capsule has a pink body and pink cap, size 4 (approx. 14.3 mm), marked “LEU” on the cap and “5” on the body with black ink.

Lenalidomide Reddy 7.5 mg hard capsules contain white to yellow coloured powder. The hard capsule has a grey body and orange cap, size 3 (approx. 15.9 mm) marked “LEU” on the cap and “7.5” on the body with black ink.

Lenalidomide Reddy 10 mg hard capsules contain white to yellow coloured powder. The hard capsule has a red body and red cap, size 2 (approx. 18.0 mm), marked “LEU” on the cap and “10” on the body with black ink.

Lenalidomide Reddy 15 mg hard capsules contain white to yellow coloured powder. The hard capsule has a pink body and grey cap, size 1 (approx. 19.4 mm), marked “LEU” on the cap and “15” on the body with black ink.

Lenalidomide Reddy 20 mg hard capsules contain white to yellow coloured powder. The hard capsule has a grey body and red cap, size 0 (approx. 21.7 mm), marked “LEU” on the cap and “20” on the body with black ink.

Lenalidomide Reddy 25 mg hard capsules contain white to yellow coloured powder. The hard capsule has an orange body and orange cap, size 0 (approx. 21.7 mm), marked “LEU” on the cap and “25” on the body with black ink.

The excipients are:
Capsule content – mannitol (E421), microcrystalline cellulose (E460), sodium croscarmellose (E468) and magnesium stearate (E470b).
Capsule shell – gelatine, titanium dioxide (E171), sodium lauryl sulphate, black iron oxide (E172) (only 2.5 mg, 7.5 mg, 15 mg and 20 mg), red iron oxide (E172) (only 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg and 25 mg) and yellow iron oxide (E172) (only 7.5 mg and 25 mg).
Printing ink - shellac (E904), black iron oxide (E172) and potassium hydroxide (E525).

The hard capsules are packed in polyvinyl aluminium oriented polyamide aluminium (PVC/Al/OPA//Al) blisters packed in a carton box.

II.2 Drug Substance

The active substance is lenalidomide, an established active substance not described in any pharmacopoeia. Lenalidomide is a crystalline powder and is well soluble in terms of the Biopharmaceutical classification system (BCS) classification system across the physiological pH range with highest solubility at low pH. Lenalidomide has one asymmetric carbon and is a racemic mixture. Polymorphic form A is used.

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.

<u>Manufacturing process</u>
The manufacturing process consists of four steps. The first three steps are true chemical transformation steps. In the final step a solvent and catalyst is used. No class 1 solvents are used in the manufacturing process. Lenalidomide has been adequately characterised and acceptable specifications for solvents and reagents have been adopted. The specifications of the starting materials, solvents and reagents are acceptable. The manufacturing process is described in sufficient detail.

Quality control of drug substance
The active substance specification has been established in-house by the MAH and is considered adequate to control the quality. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for three full scaled batches.

Stability of drug substance
Stability data on the active substance have been provided for three full scaled batches in accordance with applicable European guidelines, demonstrating the stability of the active substance for two years. Based on the data submitted, a retest period could be granted of 24 months when stored under the stated 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 drug products are hard capsules, available in seven strengths. The seven strengths can be distinguished by the colour and size of the capsule, and the printed text on the capsules.

Manufacturing process
The manufacturing process consists of dry mixing and encapsulation. The manufacturing process 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 full scaled batches per strength in accordance with the relevant European guidelines. The manufacturing process has been adequately described.

Control of excipients
The excipients comply with Ph.Eur. and in-house requirements. 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, identification, uniformity of dosage units, dissolution, related substances, assay and water content. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. No risk for formation of nitrosamines in the drug product was identified and therefore no specification for nitrosamine impurities on the final product was deemed necessary.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three full scaled batches per strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three full scaled batches per strength stored at 25°C/ 60% RH (24 months) and 40°C/75% RH (6 months). The stability was tested in accordance with applicable European guidelines. A decreasing trend in dissolution is observed for the two lower strengths at accelerated conditions. A significant change is observed in dissolution at accelerated conditions. Under long term conditions the capsules remain within specification. Data on the sensitivity to moisture show that the product does not need to be stored in the original package to protect from moisture. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. On basis of the data submitted, a shelf life was granted of 24 months. The labelled storage conditions are: "do not store above 25°C". The MAH has made a commitment to perform additional stability studies within two years of the end of the registration procedure. Stability will be tested at accelerated and, if required, at intermediate conditions to re-evaluate the storage restriction of "Do not store above 25°C". If the results at accelerated conditions are within specification, or if the results at intermediate conditions (if needed) are within specification, a variation will be submitted to amend the storage restriction accordingly.

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

Scientific data and/or certificates of suitability issued by the EDQM for gelatine 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. The other excipients are not of animal origin.

II.4 Discussion on chemical, pharmaceutical and biological aspects

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

The following post-approval commitments were made:

- Perform additional stability studies within two years of the end of the registration procedure to re-evaluate the storage restriction of "Do not store above 25°C".

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Lenalidomide Reddy is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was 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 was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was 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 member states agreed that no further clinical studies are required, besides the two bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test product Lenalidomide Reddy 2.5 mg and 25 mg hard capsules (Reddy Holding GmbH, Germany) was compared with the pharmacokinetic profile of the reference product Revlimid 25 mg and 2.5 mg hard capsules (Bristol-Myers Squibb Pharma EEIG, Ireland).

The choice of the reference products in the bioequivalence studies have been justified by comparison of dissolution study results and composition. *In vitro* dissolution profiles were investigated for all strengths at three pH-values according to the EMA Bioequivalence guideline. The results at pH 1.2 and pH 4.5 show that more than 85% of the amount of drug added was dissolved within 15 minutes; therefore, a f2 value is not applicable. For dissolution at pH 4.5, the f2 value was calculated. The calculated f2 similarity factor values were within criteria (>50%). An f2 value between 50 and 100% suggests that the two dissolution profiles are similar. Based on the results, the dissolution profiles are considered similar.

Biowaiver
A biowaiver was requested for Lenalidomide Reddy 5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg hard capsules.

The following general requirements must be met where a waiver for additional strength is claimed, according to the EMA Bioequivalence guideline:)

a. the pharmaceutical products are manufactured by the same manufacturing process,
b. the qualitative composition of the different strengths is the same,
c. the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all

strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule),

d. appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

Based on the manufacturing procedure, capsule composition and comparative dissolution data (pHs 1.2, 2.0, 4.5 and 6.8) a biowaiver can be granted for the additional strengths Lenalidomide Reddy 5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg hard capsules, referring to the demonstrated bioequivalence for the 25 mg strength with the reference product.

Bioequivalence studies

Study 1 – 2.5 mg, single dose, under fasting conditions

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover open label bioequivalence study was carried out under fasted conditions in 32 healthy male subjects, aged 22-44 years. Each subject received a single dose (2.5 mg) of one of the two lenalidomide formulations. The capsule was orally administered with 240 mL water after an overnight for at least 10 hours. There were two dosing periods, separated by a washout period of two days.

Blood samples were collected pre-dose and at 0.167, 0.333, 0.5, 0.667, 0.833, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 15, 18 and 24 hours after administration of the products.

The design of the study is acceptable.

Lenalidomide may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of lenalidomide. Therefore, a food interaction study is not deemed necessary. 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

32 subjects enrolled in the study. One subject had an adverse event (increased white blood count) before dosing of period 2 and was therefore withdrawn from the study. 31 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of lenalidomide, 2.5 mg under fasted conditions.

Treatment N= 31	**AUC_{0-t}** (ng.h/mL)	**$AUC_{0-\infty}$** (ng.h/mL)	**C_{max}** (ng/mL)	**t_{max}** (h)
Test	235.6 ± 50.8	240.3 ± 51.9	68.1 ± 18.9	0.667 (0.33 - 2.00)
Reference	232.6 ± 42.8	237.7 ± 43.7	66.8 ± 11.5	0.833 (0.33 - 1.25)
***Ratio (90% CI)**	1.01 (0.98 – 1.04)	-	1.00 (0.91 – 1.10)	-

$AUC_{0-\infty}$	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 the last measurable plasma concentration
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Study 2 – 25 mg, single dose, under fasting conditions

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover open label bioequivalence study was carried out under fasted conditions in 32 healthy male subjects, aged 20-43 years. Each subject received a single dose (25 mg) of one of the two lenalidomide formulations. The capsule was orally administered with 240 mL water after an overnight fast of at least 10 hours. There were two dosing periods, separated by a washout period of two days.

Blood samples were collected pre-dose and at 0.167, 0.333, 0.5, 0.667, 0.833, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 15, 18 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

32 subjects enrolled in the study. 32 subjects were eligible for pharmacokinetic analysis.

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

Treatment N= 32	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	1940.8 ± 307.2	1962.1 ± 311.4	585.3 ± 155.8	0.833 [0.50 - 2.50]
Reference	1903.3 ± 297.1	1925.6 ± 301.3	513.5 ± 134.9	0.833 [0.50 - 2.00]
***Ratio (90% CI)**	1.02 (1.00 – 1.04)	-	1.14 (1.06 - 1.23)	-

$AUC_{0-\infty}$	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 the last measurable plasma concentration
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Conclusion on bioequivalence studies:
The 90% confidence intervals calculated in study 1 and study 2 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 Reddy 2.5 mg is considered bioequivalent with Revlimid 2.5 mg and Lenalidomide Reddy 25 mg is considered bioequivalent with Revlimid 25 mg.

The results of study 1 and 2 with the 2.5 mg and 25 mg formulations can be extrapolated to strengths: 5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

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 Lenalidomide Reddy.

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

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

The summary of safety concerns is in line with that of the reference product Revlimid.

<u>Pharmacovigilance Plan</u>
The MAH shall agree the details of a controlled distribution system with the National Competent Authorities and must implement such programme nationally to ensure that:
Prior to prescribing (and where appropriate, and in agreement with the National Competent Authority, prior to dispensing) all healthcare professionals who intend to prescribe (and dispense) Lenalidomide Reddy are provided with a physician information pack containing the following:

- Educational Healthcare Professional's kit
- Educational brochures for Patients
- Patient cards
- Summary of Product Characteristics (SmPC) and Package Leaflet and Labelling.

The MAH shall implement a pregnancy prevention programme (PPP) in each Member State. Details of the PPP should be agreed with the National Competent Authorities in each Member State and put in place prior to the marketing of the product.

The MAH should agree the final text of the physician information pack contents with the National Competent Authority in each Member State and ensure that the materials contain the key elements as described below.

The MAH should agree on the implementation of the patient card system in each Member State.

The Educational Healthcare Professionals' Kit shall contain the following elements:

- Brief background on lenalidomide and its licensed indication
- Posology
- Maximum duration of treatment prescribed according to the approved indications dosing regimens

  - 4 weeks treatment for women with childbearing potential;
  - 12 weeks treatment for men and women without childbearing potential.
- The need to avoid foetal exposure due to teratogenicity of lenalidomide in animals and the expected teratogenic effect of lenalidomide in humans.
- Guidance on handling the blister or capsule of lenalidomide for healthcare professionals and caregiver
- Obligations of the HCP in relation to the prescribing of lenalidomide
  - Need to provide comprehensive advice and counselling to patients
  - That patients should be capable of complying with the requirements for the safe use of lenalidomide
  - Need to provide patients with appropriate patient educational brochure and patient card
- Safety advice relevant to all patients
  - Disposal of unwanted medicine
  - Local country specific arrangements for a prescription for lenalidomide to be dispensed
  - Description of risk of tumour flare reaction in MCL patients
  - Description of the risk of progression to AML in MDS patients including incidence rates from clinical trials
  - Description of risk of SPM
- Description of the PPP and categorisation of patients based on sex and childbearing potential
  - Algorithm for implementation of the PPP
  - Definition of women of childbearing potential (WCBP) and actions the physician should take if unsure
- Safety advice for women of childbearing potential
  - The need to avoid foetal exposure
  - Description of the PPP
  - Need for adequate contraception (even if woman has amenorrhoea) and
  - definition of adequate contraception
  - Pregnancy test regime
    - Advice on suitable tests
    - Before commencing treatment
    - During treatment based on method of contraception
    - After finishing treatment
  - Need to stop lenalidomide immediately upon suspicion of pregnancy
  - Need to tell treating doctor immediately upon suspicion of pregnancy
- Safety advice for men
  - The need to avoid foetal exposure
  - The need to use condoms if sexual partner is pregnant or a WCBP not using effective contraceptives (even if man has had a vasectomy)

        - During lenalidomide treatment
        - For at least 7 days following final dose.
    - That if his partner becomes pregnant whilst he is taking lenalidomide or shortly after he has stopped taking lenalidomide he should inform his treating doctor immediately
- Requirements in the event of pregnancy
    - Instructions to stop lenalidomide immediately upon suspicion of pregnancy, if female patient
    - Need to refer to physician specialised or experienced in dealing with teratology and its diagnosis for evaluation and advice
    - Local contact details for reporting of any suspected pregnancy
    - Pregnancy reporting form
- Check list for physicians ensuring that patients receive the appropriate counselling concerning the treatment, contraceptive methods and pregnancy prevention appropriate for their sex and childbearing status at treatment initiation.
- Adverse event reporting forms

The Educational brochures for patients should be of 3 types:

- Brochure for women patients of childbearing potential
- Brochure for women patients who are not of childbearing potential
- Brochure for male patients

All patient brochures should contain the following elements:

- That lenalidomide is teratogenic in animals and is expected to be teratogenic in humans
- Description of the patient card and its necessity
- Disposal of unwanted medicine
- Guidance on handling lenalidomide for patients, caregivers and family members
- National or other applicable specific arrangements for a prescription for lenalidomide to be dispensed
- That the patient should not give lenalidomide to any other person
- That the patient should not donate blood during therapy (including during dose interruptions) and for at least 7 days after discontinuation of lenalidomide treatment
- That the patient should tell their doctor about any adverse events
- The following information should also be provided in the appropriate brochure:

Brochure for women patients with childbearing potential:

- The need to avoid foetal exposure
- Description of the PPP
- Need for adequate contraception and definition of adequate contraception

- Pregnancy test regime
    - Before commencing treatment
    - During treatment, at least every 4 weeks except in case of confirmed tubal sterilization
    - After finishing treatment
- The need to stop lenalidomide immediately upon suspicion of pregnancy
- The need to contact their doctor immediately upon suspicion of pregnancy

Brochure for male patients:

- The need to avoid foetal exposure
- The need to use condoms if sexual partner is pregnant or a WCBP not using effective contraception (even if the man has had vasectomy)
    - During lenalidomide treatment
    - For at least 7 days following final dose
- That if his partner becomes pregnant he should inform his treating doctor immediately
- That he should not donate semen or sperm during therapy (including during dose interruptions) and at least for 7 days after discontinuation of lenalidomide treatment

Patient Card:

- The patient card shall contain the following elements:
- Verification that appropriate counselling has taken place
- Documentation of childbearing status potential
- Pregnancy test dates and results

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 two bioequivalence studies 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 MAH proposes two separate designs for the PL: a 'Reddy' design and a 'Betapharm' design. The MAH has therefore submitted two bridging reports, one for each design. For the

text and safety information, both reports make reference to Revlimid, EMEA/H/C/000717. This bridging was found justified and acceptable.

For design and layout of the leaflet of the 'Reddy' design, a user consultation with target patient groups on the package leaflet (PL) has been performed for on the basis of a bridging report making reference to Imatinib, DE/H/4068/001-003/DC. The bridging report submitted by the MAH has been found acceptable; bridging is justified.

For design and layout of the leaflet of the 'Betapharm' design, 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 Naratriptan beta bei Migräne, DE/H/6390/001/DC. The bridging report submitted by the MAH has been found acceptable; bridging is justified.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Lenalidomide Reddy 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg and 25 mg hard capsules have a proven chemical-pharmaceutical quality and are generic forms of Revlimid 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg and 25 mg hard capsules. Revlimid is a well-known medicinal product with an established favourable efficacy and safety profile.

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 Reddy with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 27 April 2023.

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
-	-	-	-	-	-