LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Lenalidomide Orion
(lenalidomide)

SE/H/2033/01-05/DC

This module reflects the scientific discussion for the approval of Lenalidomide Orion. The procedure was finalised on 2020-12-15. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Lenalidomide Orion, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, Capsule, hard.

The active substance is lenalidomide. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Lenalidomide Orion, 5mg, 10 mg, 15 mg, 20 mg and 25 mg, capsule, hard, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Orion Corporation, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and Denmark, Finland and Norway as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Revlimid, 25 mg, capsule, hard, authorised in the European Union since 2007, with Celgene Europe Limited as marketing authorisation holder.

The reference product used in the bioequivalence study is Revlimid, 25 mg, capsule, hard, from Norway with Celgene Europe Limited as marketing authorisation holder.

Potential similarity with orphan medicinal products

Having considered the arguments presented by the applicant and with reference to Article 8 of Regulation (EC) No 141/2000, Lenalidomide Orion is considered not similar (as defined in Article 3 of Commission Regulation (EC) No. 847/2000) to Kyprolis, Imnovid, Ninlaro, Farydak, Darzalex, Gazyvaro, Imbruvica, Reblozyl, Blenrep or Tecartus.

Therefore, with reference to Article 8 of Regulation (EC) No. 141/2000, the existence of any market exclusivity for Kyprolis, Imnovid, Ninlaro, Farydak, Darzalex and Blenrep in the treatment of Multiple Myeloma, does not prevent the granting of the marketing authorisation of Lenalidomide Orion. This finding is without prejudice to the outcome of the scientific assessment of the marketing authorisation application.

Therefore, with reference to Article 8 of Regulation (EC) No. 141/2000, the existence of any market exclusivity for Gazyvaro in the treatment of Follicular Lymphoma, does not prevent the granting of the marketing authorisation of Lenalidomide Orion. This finding is without prejudice to the outcome of the scientific assessment of the marketing authorisation application.

Therefore, with reference to Article 8 of Regulation (EC) No. 141/2000, the existence of any market exclusivity for Imbruvica or Tecartus in the treatment of Mantle cell lymphoma, does not prevent the granting of the marketing authorisation of Lenalidomide Orion. This finding is without prejudice to the outcome of the scientific assessment of the marketing authorisation application.

Therefore, with reference to Article 8 of Regulation (EC) No. 141/2000, the existence of any market exclusivity for Reblozyl in the treatment of Myelodysplastic syndrome, does not prevent the granting of the marketing authorisation of Lenalidomide Orion. This finding is without prejudice to the outcome of the scientific assessment of the marketing authorisation application.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of lenalidomide are well known. As lenalidomide is a widely used, well-known active substance, no further non-clinical studies with the active pharmaceutical ingredient (API) are required. Overview based on literature review is, thus, appropriate.

During genotoxicity screening of substances which are used or might be formed during the synthesis of lenalidomide, the compounds AC.1303, AC2087, AC.203, K/1502 and K/1504 were regarded as Potential Genotoxic Impurities (PGI). To evaluate their mutagenicity *in vitro*, Bacterial Reverese Mutation (AMES) tests were performed. The impurities were tested in the Bacterial Reverse Mutation assay using Salmonella typhimurium strains TA98, TA100, TA102, TA1535 and TA97a or Escherichia Coli WP2uvrA, in the presence or absence of metabolic activation. Racemic nitrolenamide (K/1504.) was not mutagenic whereas 2-Methyl-3-aminobenzoic acid (AC.2103), 2-methyl 3-amino-2-methylbenzoate (AC.2087), methyl-nitrobenzoate (AC.1303) and lenahydroxylamine (K#1502) were mutagenic.

A justification for proposed impurity limits in the drug product is included in the quality part of the dossier and the specifications of these compounds are according to the ICH guidelines for impurities. This is considered acceptable.

Environmental Risk Assessment (ERA)
Since Lenalidomide Orion is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Lenalidomide Orion from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted one bioequivalence study comparing Lenalidomide Orion with the reference product Revlimid.

Pharmacokinetic properties of the active substance

Absorption:
Lenalidomide is rapidly absorbed following oral administration in healthy volunteers, under fasting conditions, with maximum plasma concentrations occurring between 0.5 and 2 hours post-dose.

Co-administration with a high-fat and high-calorie meal in healthy volunteers reduces the extent of absorption, resulting in an approximately 20% decrease in AUC and 50% decrease in C_{max} in plasma. However, in the main multiple myeloma and myelodysplastic syndromes registration trials where the efficacy and safety were established for lenalidomide, the medicinal product was administered without regard to food intake. Thus, lenalidomide can be administered with or without food.

Linearity:
In patients, as well as in healthy volunteers, the maximum concentration (C_{max}) and the area under the concentration versus time curve (AUC) increase proportionally with increases in dose.

Elimination:
At doses of 5 to 25 mg/day, half-life in plasma is approximately 3 hours in healthy volunteers.

Methods
This was a single-dose, two-way crossover study conducted in 26 healthy volunteers, comparing Lenalidomide Orion, 25 mg capsule with Revlimid, 25 mg capsule under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 24 hours post-dose. Plasma concentrations of lenalidomide were determined with an LC/MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}. The study was conducted between January 16 and February 8, 2016.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 1 below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for substance, n=26.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**1339.8 (±231.7)**	**418.2 (±115.2)**	**0.83 (0.50-2.00)**
Reference	**1360.2 (±248.1)**	**417.2 (±130.6)**	**0.67 (0.50-2.33)**
***Ratio (90% CI)**	**98.63 (96.16-101.16)**	**100.88 (94.55-107.63)**	
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 plasma concentration			

**calculated based on ln-transformed data*

For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell

within the conventional acceptance range of 80.00-125.00%.

A biowaiver was sought for the additional strengths of 5, 7.5, 10, 15 and 20 mg.

Discussion and overall conclusion
The bioequivalence study and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr). The bioanalytical methods were adequately validated. The study design is also in accordance with the product-specific bioequivalence guidance of Lenalidomide (EMA/CHMP/177335/2016/Corr.) which states that the 25 mg dose should be used and that the study should be performed under fasting conditions.

Absence of studies with the additional strengths of 5, 7.5, 10, 15 and 20 mg is acceptable, as all conditions for biowaiver for additional strengths, as described in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) are fulfilled and since the pharmacokinetics of lenalidomide is linear between 5 mg and 25 mg.

Based on the submitted bioequivalence study, Lenalidomide Orion is considered bioequivalent with Revlimid.

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

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 Lenalidomid Orion.

Safety specification

The MAH has submitted the version 1.2 RMP dated 22 Oct 2020 and proposed the following summary safety concerns:

Summary of safety concerns	
Important identified risks	• Teratogenicity • Serious Infection due to Neutropenia • Second Primary Malignancy (SPM) • Tumour Flare Reaction (TFR) (risk related to Indications/Target Population Mantle cell lymphoma (MCL) and Follicular lymphoma (FL))
Important potential risks	• Cardiac failure • Cardiac arrhythmias • Ischaemic heart disease (including myocardial infarction) • Off-label use
Missing information	None

Pharmacovigilance Plan

Routine pharmacovigilance is suggested, and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

The applicant has suggested the following risk minimisation activities (the table is a collapsed version):

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risk		
Teratogenicity	Routine risk minimisation measures: SmPC sections 4.3, 4.4 and 4.6, 4.8, 5.3 and 6.6. PL section 2 and 3. *Warning in the outer package:* "WARNING: Risk of severe birth defects. Do not use while pregnant or breastfeeding. You must follow the Pregnancy Prevention Programme." *Pack size:* The pack is based on a maximum 4-week supply of capsules to ensure that females of child-bearing potential are required to obtain a new monthly prescription with a medically supervised pregnancy test. *Legal status:* Restricted medical prescription and distribution concerning patients with child-bearing potential. Additional risk minimisation measures: • Educational material for healthcare professionals Including DHCP • Patient educational material • Patient card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: This medicinal product is subject to additional monitoring. Specific adverse drug reaction follow-up questionnaire.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Serious Infection due to Neutropenia	Routine risk minimisation measures: SmPC sections 4.2, 4.4 and 4.8 PL section 2 and 4. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: This medicinal product is subject to additional monitoring. Specific adverse drug reaction follow-up questionnaire.
Second Primary Malignancy (SPM)	Routine risk minimisation measures: SmPC sections 4.4 and 4.8. PL sections 2 and 4. Additional risk minimisation measures: • Educational material for healthcare professionals including DHCP	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: This medicinal product is subject to additional monitoring. Specific adverse drug reaction follow-up questionnaire.
Tumour Flare Reaction (TFR) (risk related to Indications/Target Population Mantle cell lymphoma (MCL) and Follicular lymphoma (FL))	Routine risk minimisation measures: SmPC sections 4.2, 4.4 and 4.8. PL sections 2 and 4. Additional risk minimisation measures: • Educational material for healthcare professionals including DHPC	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: This medicinal product is subject to additional monitoring. Specific adverse drug reaction follow-up questionnaire.
Cardiac failure	Routine risk minimisation measures: SmPC section 4.8 PL section 4. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: This medicinal product is subject to additional monitoring. Specific adverse drug reaction follow-up questionnaire.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Cardiac arrhythmias	Routine risk minimisation measures: SmPC section 4.8 PL section 4. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: This medicinal product is subject to additional monitoring. Specific adverse drug reaction follow-up questionnaire.
Ischaemic heart disease (including myocardial infarction)	Routine risk minimisation measures: SmPC sections 4.4 and 4.8. PL sections 2 and 4. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: This medicinal product is subject to additional monitoring. Specific adverse drug reaction follow-up questionnaire.
Off-label use	Routine risk minimisation measures: SmPC section 4.4. Additional risk minimisation measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: This medicinal product is subject to additional monitoring.

Assessor's comment Day 70:
The Risk minimisation measures are acceptable.

Summary of the RMP
The submitted Risk Management Plan, version 1.2 signed 22 Oct 2020 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Revlimid, EMEA/H/C/000717 and Buranagel, DE/H/5281/01/DC. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Lenalidomide Orion, is found adequate. There are no objections to approval of Lenalidomide Orion, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

Additional risk minimisation measures (including educational material)>
The applicant has proposed the following key elements. These are identical, where relevant, with the reference product Revlimid and are acceptable.

1. 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 launch, all doctors who intend to prescribe Lenalidomide Orion and all pharmacists who may dispense Lenalidomide Orion receive a Direct Healthcare Professional Communication as described below.
- 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 Orion are provided with a physician information pack containing the following:
    - o Educational health care professional's kit
    - o Educational brochures for patients
    - o Patient cards
    - o Summary of product characteristics (SmPC) and package leaflet and labelling.

2. 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 launch of the product.

3. The MAH should agree the final text of the Direct Healthcare Professional Communication and 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.

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

Key messages of the additional risk minimisation measures

Direct Healthcare Professional Communications
The Direct Healthcare Professional Communication prior to launch shall consist of two parts:
- National specific requirements agreed with the National Competent Authority regarding:
    - o Distribution of the product
    - o To ensure that all appropriate measures have been performed prior to Lenalidomide Orion being dispensed

The Educational Healthcare Professional's Kit
The Educational Health Care Professional's 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 including a summary of the results of study CC-5013-TOX-004
- Guidance on handling the blister or capsule of Revlimid for healthcare professionals and caregivers
- Obligations of the health care professional in relation to the prescribing of Lenalidomide Orion
  - 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 Orion
  - Need to provide patients with appropriate patient educational brochure and patient card

- <u>Safety advice relevant to all patients</u>
  - Disposal of unwanted medicine
  - Local country specific arrangements for a prescription for Lenalidomide Orion 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
- <u>Description of the PPP and categorisation of patients based on sex and childbearing potential</u>
  - Algorithm for implementation of PPP
  - Definition of women of childbearing potential (WCBP) and actions the physician should take if unsure

- <u>Safety advice for women of childbearing potential</u>
  - 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 Orion immediately upon suspicion of pregnancy
  - Need to tell treating doctor immediately upon suspicion of pregnancy

- <u>Safety advice for men</u>
  - The need to avoid foetal exposure
  - The need to use condoms if sexual partner is pregnant or a WCBP not using effective contraceptions (even if man has had a vasectomy)
    - During Lenalidomide Orion treatment
    - For at least 7 days following final dose.
  - That if his partner becomes pregnant whilst he is taking Lenalidomide Orion or shortly after he has stopped taking Lenalidomide Orion he should inform his treating doctor immediately

- <u>Requirements in the event of pregnancy</u>
  - Instructions to stop Lenalidomide Orion 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

Educational Brochures for patients

- 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 Orion to be dispensed
  - That the patient should not give Lenalidomide Orion 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 Orion 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 Orion 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 contraceptions (even if man has had vasectomy)
    - During Lenalidomide Orion 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 Orion 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

VII. APPROVAL

The decentralised procedure for Lenalidomide Orion, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, Capsule, hard was positively finalised on 2020-12-15.

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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