LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Lenalidomide Newbury
(lenalidomide)

SE/H/2413/002,004,005,007

This module reflects the scientific discussion for the approval of Lenalidomide Newbury. The Public Assessment Report was written in December 2021 by the previous RMS (IS) after initial procedure (IS/H/0468/001-007/DC) and is attached at the end of this document. RMS transfer from (IS) to SE was completed 2023-02-23. For information on changes after this date please refer to the module 'Update'.

Active substance	lenalidomide
Pharmaceutical form	Capsule, hard
Strength	5 mg; 10 mg; 15 mg; 25 mg
Applicant	Newbury Pharmaceuticals AB
EU-Procedure number (original)	IS/H/0468/002;004;005;007/DC

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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CMDh/223/2005
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Public Assessment Report

Scientific discussion

Lenalidomide Newbury lenalidomide

IS/H/0468/001-007/DC

Date: 29.12.2021

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This module reflects the scientific discussion for the approval of Lenalidomide Newbury. The procedure was finalised at 20.Des.2021. 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, the Member States have granted a marketing authorisation for Lenalidomide Newbury, hard capsule, 2.5 mg, 5.0 mg, 7.5 mg, 10 mg, 15 mg, 20 mg and 25 mg, from Newbury Pharmaceuticals AB.

The product is indicated for:

Multiple myeloma
[Product Name] as monotherapy is indicated for the maintenance treatment of adult patients with newly diagnosed multiple myeloma who have undergone autologous stem cell transplantation.

[Product Name] as combination therapy with dexamethasone, or bortezomib and dexamethasone, or melphalan and prednisone (see section 4.2) is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant.

[Product Name] 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
[Product Name] 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
[Product name] as monotherapy is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (see sections 4.4 and 5.1).

Follicular lymphoma
[Product name] 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 indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to insert Article 10(1) of Directive 2001/83/EC.

Lenalidomide binds directly to cereblon, a component of a cullin ring E3 ubiquitin ligase enzyme complex that includes deoxyribonucleic acid (DNA) damage-binding protein 1(DDB1), cullin 4 (CUL4), and regulator of cullins 1 (Roc1). In haematopoietic cells, lenalidomide binding to cereblon recruits substrate proteins Aiolos and Ikaros, lymphoid transcriptional factors, leading to their ubiquitination and subsequent degradation resulting in direct cytotoxic and immunomodulatory effects.

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Specifically, lenalidomide inhibits proliferation and enhances apoptosis of certain haematopoietic tumour cells (including MM plasma tumour cells, follicular lymphoma tumour cells and those with deletions of chromosome 5), enhances T cell- and Natural Killer (NK) cell-mediated immunity and increases the number of NK, T and NK T cells. In MDS Del (5q), lenalidomide selectively inhibits the abnormal clone by increasing the apoptosis of Del (5q) cells.
The combination of lenalidomide and rituximab increases ADCC and direct tumor apoptosis in follicular lymphoma cells.
The lenalidomide mechanism of action also includes additional activities such as anti-angiogenic and pro-erythropoietic properties. Lenalidomide inhibits angiogenesis by blocking the migration and adhesion of endothelial cells and the formation of microvessels, augments foetal haemoglobin production by CD34+ haematopoietic stem cells, and inhibits production of pro-inflammatory cytokines (e.g., TNF-α and IL-6) by monocytes.

No discussions were held with CMDh during the procedure.

II. QUALITY ASPECTS

II.1 Introduction

The drug product is an immediate release hard capsule containing the active substance lenalidomide, together with the excipients lactose anhydrous, cellulose microcrystalline, croscarmellose sodium and magnesium stearate in the capsule shell. Two product groups are proposed: Group A (15, 20 and 25 mg) and Group B (2.5, 5, 7.5 and 10 mg). Within each group, the composition of the different strengths is dose proportional. The hard capsules are packed into PVC/Aclar/Al blister packs. The excipients and container closure systems are common for this type of dosage form.

Drug composition

Capsule contents
Lactose
Cellulose, microcrystalline (E460)
Croscarmellose sodium (E468)
Magnesium stearate (E470b)

Capsule shell
[Product Name] 2.5 mg hard capsules
Brilliant Blue FCF (E133)
Erythrosine (E127)
Allura Red AC (E129)
Red iron oxide (E172)
Yellow iron oxide (E172)
Titanium dioxide (E171)
Gelatin

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[Product Name] 5 mg hard capsules
Brilliant Blue FCF (E133)
Sunset Yellow FCF (E110)
Black iron oxide (E172)
Red iron oxide (E172)
Yellow iron oxide (E172)
Titanium dioxide (E171)
Gelatin

[Product Name] 7.5 mg hard capsules
Brilliant Blue FCF (E133)
Erythrosine (E127)
Sunset Yellow FCF (E110)
Titanium dioxide (E171)
Gelatin

[Product Name] 10 mg hard capsules
Brilliant Blue FCF (E133)
Allura Red AC (E129)
Tartrazine (E102)
Sunset Yellow FCF (E110)
Titanium dioxide (E171)
Gelatin

[Product Name] 15 mg hard capsules
Brilliant Blue FCF (E133)
Allura Red AC (E129)
Tartrazine (E102)
Black iron oxide (E172)
Red iron oxide (E172)
Yellow iron oxide (E172)
Titanium dioxide (E171)
Gelatin

[Product Name] 20 mg hard capsules
Brilliant Blue FCF (E133)
Allura Red AC (E129)
Red iron oxide (E172)
Yellow iron oxide (E172)
Titanium dioxide (E171)
Gelatin

[Product Name] 25 mg hard capsules
Titanium dioxide (E171)
Gelatin

Printing ink
Shellac
Propylene glycol (E1520)
Black iron oxide (E172)
Potassium hydroxide (E525)
Strong ammonia solution (E527)

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II.2 Drug Substance

The drug substance, Lenalidomide is an established drug substance; however, it is not subject of a monograph in the Ph.Eur. and no draft monograph is available so far. The ASMF procedure is used (Applicant´s Part:
MLL/LEN/AP/002/05/JULY.2021; Restricted Part: MLL/LEN/RP/002/05/JULY.2021).

Lenalidomide is an off-white to pale yellow powder and classified as BCS class III drug substance, due to its high solubility and low permeability.

The active substance specification includes relevant tests and the acceptance limits have been appropriately justified. The analytical methods applied are suitably described and validated as ASMF for the active substance confirms.

Stability studies have been conducted and the data provided is sufficient to support the proposed retest period.

II.3 Medicinal Product

The development of the drug product formulation is well described. The excipients used in the product are all standard in the manufacture of immediate release hard capsule and are compliant with European Pharmacopoeia (or equivalent) requirements.

The standard manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

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

Stability studies under ICH conditions have been performed in the commercial packaging and data presented support the shelf life claimed in the SPC; 3 years. This medicinal product does not require any special storage conditions.

The pharmaceutical quality of Lenalidomide Newbury has been adequately shown.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of active substance and medicinal product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics.

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III. NON-CLINICAL ASPECTS

III.1 Introduction

Abridged applications avoid the need for repetitive tests on animals and humans.

III.2 Pharmacology, Pharmacokinetics and Toxicology

Pharmacodynamic, pharmacokinetic and toxicological properties of lenalidomide are well known. As lenalidomide is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

III.3 Ecotoxicity/environmental risk assessment (ERA)

Since Lenalidomide Newbury 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.4 Discussion on the non-clinical aspects

Lenalidomide Newbury is a generic to Revlimid from Bristol-Myers Squibb Pharma EEIG. The marketing authorisation for the reference medicinal product was granted on 14.06.2007 and a MAH transfer was performed from Celgene to Bristol-Myers in 2020. Abridged applications avoid the need for repetitive tests on animals and humans.

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

IV. CLINICAL ASPECTS

IV.1 Introduction

Abridged applications avoid the need for repetitive tests on animals and humans apart from a conduction of a bioequivalence study to confirm that the applied product is bioequivalent to the reference medicinal product.

The clinical overview on the clinical pharmacology, efficacy and safety is adequate.

IV.2 Pharmacokinetics

Relevant for the assessment are the Guideline on the Investigation of Bioequivalence

(CPMP/EWP/QWP/1401/98), Lenalidomide hard gelatine capsules 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg and 25 mg product-specific bioequivalence guidance* (EMA/CHMP/177335/2016/Corr.†) as well as the Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/09).

Biowaiver

Two bioequivalence studies were submitted. A study on the 10 mg strength to support a biowaiver for the 2.5 mg, 5 mg and 7.5 mg strengths (referred to as the 10 mg series) and a study on the 25 mg strength to support a biowaiver for the 15 mg and 20 mg strengths (referred to as the 25 mg series). A biowaiver for the 10 mg series and the 25 mg series is appropriate. The pharmacokinetics are linear for the proposed dosing range (2.5 mg to 25 mg). All of the remaining criteria for a biowaiver have been met i.e.: the products are manufactured by the same manufacturing process; the qualitative composition within the 10 mg series and within the 25 mg series is the same; the composition within the 10 mg series and within the 25 mg series are quantitatively proportional,; and in vitro dissolution profiles are comparable.

Bioequivalence studies

To support the application, the applicant has submitted as report two bioequivalence studies, Study No. NCS-467-16-CS and Study No. NCS-468-16-CS

Statement of GCP compliance is provided. A statement is provided to confirm that the bioequivalence study carried out outside the European Union meets the ethical requirements of the European Union Directive 2001/20/EC.

The study No. NCS-467-16-CS The study was an open label, randomised, balanced, single dose, 2-period, 2-sequence, crossover bioequivalence study comparing two 10 mg hard capsules of lenalidomide formulations in healthy adult male subjects under fasting conditions. The study was conducted under standardised conditions. Lenalidomide was measured in human plasma using a validated LC/MS/MS method. The test to reference ratio of geometric LSmeans and corresponding 90% confidence interval for the C_{max} and AUC_{0-t} were all within the acceptance range of 80.00 to 125.00%. The drugs were generally safe and well tolerated by the subjects included in the study.

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

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h
Test	746.669 ±103.956	766.669 ±103.609	217.397 ±60.762	0.750 (0.500, 2.000)
Reference	751.838 ±121.691	771.488 ±122.352	219.050 ±53.433	0.750 (0.500, 1.500)
***Ratio (90% CI)**	99.13 (94.86- 103.60)	-	97.72 (86.95- 109.82)	

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.
AUC_{0-72h} can be reported instead of AUC_{0-t}, in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products

$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.
$AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}

C_{max} Maximum plasma concentration

t_{max} Time until Cmax is reached

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**ln-transformed values*

The study No. NCS-468-16-CS was an open label, randomised, single dose, 2-period, 2-sequence, crossover bioequivalence study comparing two 25 mg hard capsules of lenalidomide formulations in healthy adult male subjects under fasting conditions. The study was conducted under standardised conditions. Lenalidomide was measured in human plasma using a validated LC/MS/MS method. The test to reference ratio of geometric LSmeans and corresponding 90% confidence interval for the C_{max} and AUC_{0-t} were all within the acceptance range of 80.00 to 125.00%. The drugs were generally safe and well tolerated by the subjects included in the study

Treatment	**AUC_{0-t}** **ng/ml/h**	**$AUC_{0-\infty}$** **ng/ml/h**	**C_{max}** **ng/ml**	**t_{max}** **h**
Test	1936.040 ± 344.026	1953.526 ± 348.965	511.783 ± 119.296	0.750 (0.500, 3.000)
Reference	1957.865 ± 385.913	1977.360 ± 392.000	483.358 ± 115.555	0.750 (0.500, 3.000)
***Ratio (90% CI)**	99.02 (96.78-101.32)		106.06 (97.31-115.61)	
AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t. AUC_{0-72h} can be reported instead of AUC_{0-t}, in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products **$AUC_{0-\infty}$** Area under the plasma concentration curve extrapolated to infinite time. $AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t} **C_{max}** Maximum plasma concentration **t_{max}** Time until Cmax is reached				

**ln-transformed values*

<u>Conclusion on bioequivalence studies</u>:
Based on the submitted bioequivalence study Lenalidomide Newbury is considered bioequivalent with Revlimid.

IV.3 Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

IV.4 Clinical efficacy

No new clinical efficacy studies were presented and no such studies are required for this application.

IV.5 Clinical safety

No new clinical safety studies were presented and no such studies are required for this application.

IV.6 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 Newbury.

- Summary table of safety concerns as approved in RMP

Summary of safety concerns	
Important identified risks	• Teratogenicity • Serious infection due to neutropenia • SPM (second primary malignancies) • Important Identified Risk Related to Indication/Target Population − For MCL (Mantle cell lymphoma) and FL (follicular lymphoma): TFR (Tumor Flare Reaction)
Important potential risks	• Cardiac failure • Cardiac arrhythmias • Ischaemic heart disease (including myocardial infarction) • Off-label use
Missing information	None

IV.7 Discussion on the clinical aspects

Lenalidomide Newbury is a generic to Revlimid. Abridged applications avoid the need for repetitive tests on animals and humans apart from a conduction of a bioequivalence study.

The application contains an adequate review of published clinical data and the bioequivalence has been shown between Lenalidomide Newbury and Revlimid.

Approval is recommended from the clinical point of view.

V. USER CONSULTATION

The results of the user consultation with target patient groups on the package leaflet report submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*
Assessment of the User Testing is attached in the 'QRD Guidance and Checklist for the Review of User Testing Results.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

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Based on the review of the data on quality, safety and efficacy, the risk-benefit ratio for the application for Lenalidomide Newbury, that is indicated for:

Multiple myeloma
[Product Name] as monotherapy is indicated for the maintenance treatment of adult patients with newly diagnosed multiple myeloma who have undergone autologous stem cell transplantation.

[Product Name] as combination therapy with dexamethasone, or bortezomib and dexamethasone, or melphalan and prednisone (see section 4.2) is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant.

[Product Name] 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
[Product Name] 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
[Product name] as monotherapy is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (see sections 4.4 and 5.1).

Follicular lymphoma
[Product name] in combination with rituximab (anti-CD20 antibody) is indicated for the treatment of adult patients with previously treated follicular lymphoma (Grade 1 – 3a).

It is considered positive and marketing authorisation can be recommended.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

There was no Discussion in CMDh. There are no specific obligations and follow-up measures.

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