Public Assessment Report

Scientific discussion

Lenalidomide Pharmascience lenalidomide

IS/H/0386/001-007/DC

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This module reflects the scientific discussion for the approval of Lenalidomide Pharmascience. The procedure was finalised at 17.Jul.2020. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Lenalidomide Pharmascience, hard capsules, 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 25 mg, from Pharmascience International Ltd,

The product is indicated for*:*

Multiple myeloma
Lenalidomide Pharmascience as monotherapy is indicated for the maintenance treatment of adult patients with newly diagnosed multiple myeloma who have undergone autologous stem cell transplantation.
Lenalidomide Pharmascience as combination therapy with dexamethasone, or bortezomib and dexamethasone, or melphalan and prednisone (see section 4.2 of SmPC) is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant.
Lenalidomide Pharmascience in combination with dexamethasone is indicated for the treatment of multiple myeloma in adult patients who have received at least one prior therapy.

Follicular lymphoma
Lenalidomide Pharmascience 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 Article 10(1) of Directive 2001/83/EC.

No discussions were held with CMDh during the procedure.

II. QUALITY ASPECTS

II.1 Introduction

Lenalidomide Pharmascience , immediate release hard capsules,
2.5mg/5mg/7.5mg/10mg/15mg/20mg/25mg, are packaged in PVC/Aclar/Al blister packs which are packed in pre-printed carton box with leaflet inserted.

Description of Lenalidomide hard capsules:
2.5 mg hard capsules: A dark blue opaque cap/ light orange opaque body, capsule shell size No. 4 imprinted in black ink with "LP" on the cap and "637" on the body and filled with white powder.

5 mg hard capsules: A green opaque cap/ light brown opaque body, capsule shell size No. 2 imprinted in black ink with "LP" on the cap and "638" on the body and filled with white powder.

7.5 mg hard capsules: A violet opaque cap/ pink opaque body, capsule shell size No. 1 imprinted in black ink with "LP" on the cap and "643" on the body and filled with white powder.

10 mg hard capsules: A yellow opaque cap/ gray opaque body, capsule shell size No. 0 imprinted in black ink with "LP" on the cap and "639" on the body and filled with white powder.

15 mg hard capsules: A brown opaque cap/ grey opaque body, capsule shell size No. 2 imprinted in black ink with "LP" on the cap and "640" on the body and filled with white powder.

20 mg hard capsules: A dark red opaque cap/ light gray opaque body, capsule shell size No. 1 imprinted in black ink with "LP" on the cap and "641" on the body and filled with white powder.

25 mg hard capsules: A white opaque cap/ white opaque body, capsule shell size No. 0 imprinted in black ink with "LP" on the cap and "642" on the body and filled with white powder.

Capsule contents of Lenalidomide hard capsules:
Lenalidomide
Lactose (see section 2 in SmPC)
Ceulluose microcrystalline
Croscarmellose sodium
Magnesium stearate

Capsule shell and printing ink ingredients of Lenalidomide hard capsules:
2.5 mg hard capsules: Brilliant Blue FCF (E133), Erythrosine (E127), Allura Red AC (E129) (see section 2 in SmPC), red iron oxide (E172), yellow iron oxide (E172), titanium dioxide (E171) and gelatin. Printing ink: shellac, propylene glycol (E1520), black iron oxide (E172) and potassium hydroxide.

5 mg hard capsules: Brilliant Blue FCF (E133), Sunset Yellow FCF (E110) (see section 2 in SmPC), black iron oxide (E172), red iron oxide (E172), yellow iron oxide (E172), titanium dioxide (E171) and gelatin. Printing ink: shellac, propylene glycol (E1520), black iron oxide (E172) and potassium hydroxide.

7.5 mg hard capsules: Brilliant Blue FCF (E133), Erythrosine (E127), Sunset Yellow FCF (E110) (see section 2 in SmPC), titanium dioxide (E171) and gelatin. Printing ink: shellac, propylene glycol (E1520), black iron oxide (E172) and potassium hydroxide.

10 mg hard capsules: Brilliant Blue FCF (E133), Allura Red AC (E129) (see section 2), Tartrazine (E102) (see section 2 in SmPC), Sunset Yellow FCF (E110) (see section 2), titanium dioxide (E171) and gelatin. Printing ink: shellac, propylene glycol (E1520), black iron oxide (E172) and potassium hydroxide.

15 mg hard capsules: Brilliant Blue FCF (E133), Allura Red AC (E129) (see section 2 in SmPC), Tartrazine (E102) (see section 2 in SmPC), black iron oxide (E172), red iron oxide (E172), yellow iron oxide (E172), titanium dioxide (E171) and gelatin. Printing ink: shellac, propylene glycol (E1520), black iron oxide(E172) and potassium hydroxide.

20 mg hard capsules: Brilliant Blue FCF (E133), Allura Red AC (E129) (see section 2 in SmPC), red iron oxide (E172), yellow iron oxide (E172), titanium dioxide (E171) and gelatin. Printing ink: shellac, propylene glycol (E1520), black iron oxide (E172) and potassium hydroxide.

25 mg hard capsules: Titanium dioxide (E171) and gelatin. Printing ink: shellac, propylene glycol (E1520), black iron oxide (E172) and potassium hydroxide.

II.2 Drug Substance

The drug substance is LENALIDOMIDE, an established active substance of chemical origin. It is not monographed in the European Pharmacopoeia.

Lenalidomide is off-white to pale yellow powder

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 (prolonged release hard capsules) 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. Comparative *in vitro* dissolution profiles of the generic product and the reference product support the claim for similarity.

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 and does not require any special storage conditions.

The pharmaceutical quality of Lenalidomide Pharmascience 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.

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 Pharmascience 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 Pharmascience is a generic to Revlimid. Abridged applications avoid the need for repetitive tests on animals and humans.

There are no objections to approval of Lenalidomide Pharmascience 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 bioequivalence studies 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

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

Statements of GCP and GLP compliance are 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 24 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) – Study No. NCS-467-16-CS

Treatment	AUC_{0-t} xg/ml/h	$AUC_{0-\infty}$ xg/ml/h	C_{max} xg/ml	t_{max} h
Test	746.669 ±103.956	-	217.397 ±60.762	0.750 (0.500, 2.000)
Reference	751.838 ±121.691	-	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

**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 24 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 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) – Study No. NCS-468-16-CS

Treatment	AUC_{0-t} xg/ml/h	$AUC_{0-\infty}$ xg/ml/h	C_{max} xg/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*

Conclusion on bioequivalence studies:
Based on the submitted bioequivalence study Lenalidomide Pharmascience is considered bioequivalent with Revlimid 10 mg hard capsules and Lenalidomide Alvogen 25 mg hard capsules is considered bioequivalent with Revlimid 25 mg hard capsules.

The results of study NCS-467-16-CS with 10 mg formulation CAN be extrapolated to other strengths 2.5 mg, 5 mg and 7.5 mg strengths. The results of study NCS-468-16-CS with the 25 mg formulation CAN be extrapolated to other strengths 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.

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

- Summary table of safety concerns as approved in RMP

Important identified risks	• Teratogenicity • Serious infection due to neutropenia • SPM (second primary malignancies) • Important Identified Risk Related to Indication/Target Population − 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 Pharmascience is a generic to Revlimid hard capsules. Abridged applications avoid the need for repetitive tests on animals and humans apart from a conduction of a bioequivalence studyies.

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

The results of study NCS-467-16-CS with 10 mg formulation CAN be extrapolated to other strengths 2.5 mg, 5 mg and 7.5 mg strengths. The results of study NCS-468-16-CS with the 25 mg formulation CAN be extrapolated to other strengths 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.

Approval is recommended from the clinical point of view.

V. USER CONSULTATION

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Lenalidomide Alvogen, same strengths and pharmaceutical form. Reference is made to the same product with a minor difference between the leaflets. The readability of the parent leaflet was assessed and approved in procedure IS/H/0270/001-007. The bridging report submitted by the applicant was found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the risk-benefit ratio for the application for Lenalidomide Pharmascience, in the treatment of Multiple myeloma or Follicular lymphoma (see section 4.2 in SmPC) 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.

User consultation

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.

The results 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.

The test consisted of: a pilot test with 4 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.