10 December 2020
EMA/CHMP/3806/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lenalidomide Krka

International non-proprietary name: lenalidomide

Procedure No. EMEA/H/C/005734/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Administrative information

Name of the medicinal product:	Lenalidomide Krka
applicant:	KRKA, d.d., Novo mesto Smarjeska cesta 6 8501 Novo mesto SLOVENIA
Active substance:	LENALIDOMIDE HYDROCHLORIDE MONOHYDRATE
International non-proprietary name/Common name:	lenalidomide
Pharmaco-therapeutic group (ATC Code):	immunosuppressants, other immunosuppressants (L04AX04)
Therapeutic indication(s):	<u>Multiple myeloma</u> Lenalidomide Krka as monotherapy is indicated for the maintenance treatment of adult patients with newly diagnosed multiple myeloma who have undergone autologous stem cell transplantation. Lenalidomide Krka 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. Lenalidomide Krka in combination with dexamethasone is indicated for the treatment of multiple myeloma in adult patients who have received at least one prior therapy. <u>Follicular lymphoma</u> Lenalidomide Krka in combination with

	rituximab (anti-CD20 antibody) is indicated for the treatment of adult patients with previously treated follicular lymphoma (Grade 1 – 3a).
Pharmaceutical form(s):	Capsule, hard
Strength(s):	2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg and 25 mg
Route(s) of administration:	Oral use
Packaging:	blister (OPA/Alu/PVC-PET/Alu)
Package size(s):	21 x 1 capsule (unit dose), 21 x1 capsule (unit dose) and 7 x 1 capsule (unit dose)

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List of abbreviations

AE	Adverse Event
AML	Acute Myeloid Leukaemia
ANOVA	Analysis of variance
API	Active Pharmaceutical Ingredient
ASMF	Active Substance Master File = Drug Master File
AUC_%	Extrap_obs: Residual area in percentage
AUC0-∞	Area under the plasma concentration versus time curve from time zero to infinity
AUC0-t	Area under the plasma concentration versus time curve from time zero to the last measurable plasma concentration
BA	Bioavailability
BCS	Biopharmaceutics Classification System
BE	Bioequivalence
BMI	Body Mass Index
CFU	Colony Forming Units
CI	Confidence interval
C_{max}	Maximum measured plasma concentration
$C_{max,ss}$	Maximum measured plasma concentration at steady state
C_{pd}	Minimum observed concentration prior to dosing
CPMA	Clinical Pharmacology and Medical Affairs.
CRO	Contract Research Organization
CV	Coefficient of Variation
CV	Curriculum Vitae
DAD	Diode Array Detector
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report/Record Form
EMA	European Medicines Agency
FL	Follicular Lymphoma
GCP	Good Clinical Practices
GLM	General Linear Model
GLP	Good Laboratory Practices
HBsAg	Hepatitis B surface antigen
HCP	Healthcare Professional
HPLC	High Performance Liquid Chromatography
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
ImiDs	Immunomodulatory agents (eg, thalidomide, lenalidomide, and pomalidomide)
IMP	Investigational Medicinal Product
IR	Infrared
ISCV	Intra subject coefficient of variation
ISR	Incurred Sample Reanalysis
K_2EDTA	Di Potassium Ethylene Diamine Tetraacetic Acid
LC-MS/MS	Liquid Chromatography/ Tandem Mass Spectrometry
LDPE	Low density polyethylene
LLOQ	Lower Limit of Quantification
Ln	Logarithmic value to the base '*e*'

LOD	Limit of Detection
LOQ	1) Limit of Quantification, (2) List of Questions
MA	Marketing Authorisation
MAH	Marketing Authorisation holder
MCL	Mantle Cell Lymphoma
MDS	Myelodysplastic Syndromes
MM	Multiple myeloma
MS	1) Method SOP, 2) Mass Spectrometry
MV	Method Validation
N	Number
ng / mL	Nanogram per milliliter
NMR	Nuclear Magnetic Resonance
OPA	Oriented Polyamide
PASS	Post-authorisation Safety Studies
PE	Polyethylene
PET	Polyethylene terephthalate
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic(s)
PL	Patient Leaflet
PPP	Pregnancy Prevention Programme
PROC	Procedure
PVC	Polyvinyl chloride
QP	Qualified Person
QC	Quality Control
QSAR	Quantitative structure activity relationship
Rcf	Relative Centrifugal Force
RH	Relative Humidity
RMM	Risk Minimisation Measure
RMP	Risk Management Plan
RP	Restricted Part (or Closed Part) of ASMF
RRT	Relative retention time
RSD	Relative standard deviation
SAE	Serious Adverse Event
SAS	Statistical analysis system
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SPM	Second Primary Malignancies
$T_{1/2}$	Terminal half-life
TAMC	Total Aerobic Microbial Count
TEAE	(neutrophil count decreased)
TFR	Tumour Flare Reaction
T_{max}	Time of the maximum measured plasma concentration
$T_{max,ss}$	Time of the maximum measured plasma concentration during dosing interval at steady state
TSE	Transmissible Spongiform Encephalopathy
TTC	Threshold of toxicological concern
TYMC	Total Combined Yeasts/Moulds Count
UV	Ultraviolet
XRPD	X-Ray Powder Diffraction

1. Background information on the procedure

Submission of the dossier

The applicant KRKA, d.d., Novo mesto submitted on 29 June 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Lenalidomide Krka, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 26 April 2019.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

Multiple myeloma

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

Lenalidomide Krka 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.

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

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is

composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Revlimid instead of non-clinical and clinical studies unless justified otherwise

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 8 years in the EEA:

- Product name, strength, pharmaceutical form: Revlimid, 2.5mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg & 25 mg hard capsules.
- Marketing authorisation holder: Celgene Europe BV
- Date of authorisation: 14-06-2007

- Marketing authorisation granted by:
  - Union
- Marketing authorisation number:

  2.5mg: EU/1/07/391/005, 007

  5mg: EU/1/07/391/001, 008

  7.5mg: EU/1/07/391/006, 012

  10mg: EU/1/07/391/002, 010

  15mg: EU/1/07/391/003, 011,

  20mg: EU/1/07/391/009, 013

  25mg: EU/1/07/391/004, 014

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Revlimid 2.5mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg & 25 mg hard capsules.
- Marketing authorisation holder: Date of authorisation: 14-06-2007
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number:

  2.5mg: EU/1/07/391/005, 007

  5mg: EU/1/07/391/001, 008

  7.5mg: EU/1/07/391/006, 012

  10mg: EU/1/07/391/002, 010

  15mg: EU/1/07/391/003, 011,

  20mg: EU/1/07/391/009, 013

  25mg: EU/1/07/391/004, 014

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Revlimid 5 mg hard capsule and Revlimid 25 mg hard capsule
- Marketing authorisation holder: Celgene Europe B.V.
- Date of authorisation: 14-06-2007
- Marketing authorisation granted by:
  - Union
  - Marketing authorisation number(s): EU/H/1/07/391/008 and EU/H/1/07/391/014

- Bioavailability study number(s): 19-641 (5 mg), 18-615 (25 mg)

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.This application is submitted as a multiple of Lenalidomide KrKa d.d Novo mesto simultaneously being under initial assessment in accordance with Article 82.1 of Regulation (EC) No 726/2004.

Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was: Nevenka Trsinar Brodt

The application was received by the EMA on	29 June 2020
The procedure started on	17 July 2020
The Rapporteur's first Assessment Report was circulated to all CHMP members on	21 September 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	1 October 2020
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	15 October 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	10 November 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	26 November 2020
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Lenalidomide Krka on	10 December 2020
The CHMP adopted a report on similarity of Lenalidomide Krka with Ninlaro, Kyprolis, Farydak, Imnovid, Darzalex, Reblozyl, Gazyvaro and Blenrep on	10 December 2020

2. Scientific discussion

Introduction

The application is a duplicate of Lenalidomide KrKa d.d Novo mesto (procedure EMEA_H_C_005348) Differences only occur in procedure specific documents related to different indications.

This centralised application concerns a generic application according to article 10(1) of Directive 2001/83/EC for Lenalidomide 2.5mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg & 25 mg hard capsules. The originator product is Revlimid 2.5mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg & 25 mg hard capsules. Lenalidomide was first approved in Europe on 14 June 2007 as Revlimid 5 mg, 10 mg, 15 mg, 25 mg (MAA No: EU/1/07/391/001-004, Celgene Europe Limited, UK).

The applicant performed two pivotal bioequivalence studies between Lenalidomide Krka d.d. hard capsules in strength of 5 mg and 25 mg and reference product Revlimid hard capsules 5 mg and 25 mg, Celgene Europe Limited in order to assess bioequivalence between the products and requested a waiver for the in vivo studies on the remaining strengths 2.5mg, 7.5 mg, 10 mg, 15 mg, and 20 mg.

Proposed indications:

Multiple myeloma (MM)

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

Lenalidomide Krka 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 Krka 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 (FL)

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

Quality aspects

2.2.1. Introduction

The finished product is presented as hard capsules containing 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg and 25 mg of lenalidomide. The product contains the lenalidomide hydrochloride monohydrate.

Other ingredients are:

Capsule contents: mannitol (E421), microcrystalline cellulose (E460), pregelatinised maize starch, tartaric acid (E334) and glycerol dibehenate.

Capsule shell: hypromellose type 2910, carrageenan (E407), potassium chloride (E508), titanium dioxide (E171), yellow iron oxide (E172) (except 5 mg hard capsule), indigo carmine (E132) (except 7.5 mg and 25 mg hard capsule), red iron oxide (E172) (except 2.5 mg, 5 mg and 20 mg hard capsule), black iron oxide (E172) (except 2.5 mg, 5 mg and 20 mg hard capsule).

Imprinting ink: shellac (E904), black iron oxide (E172) (except 7.5 mg, 10 mg and 25 mg hard capsule), povidone (except 2.5 mg, 5 mg, 15 mg and 20 mg hard capsule), titanium dioxide (E171) (except 2.5 mg, 5 mg, 15 mg and 20 mg hard capsule).

The product is available in OPA/Al/PVC//PET/Al peel open, unit dose blisters, as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of lenalidomide hydrochloride monohydrate is 3-(4-amino-1-oxo-1,3-dihydro-2*H*-isoindol-2-yl)piperidine-2,6-dione hydrochloride monohydrate or 3-(4-amino-1-oxoisoindolin-2-yl)piperidine-2,6-dione hydrochloride monohydrate, corresponding to the molecular formula $C_{13}H_{13}N_3O_3.HCl.H_2O$. Lenalidomide hydrochloride monohydrate has a relative molecular mass of 313.6 g/mol and the following structure:

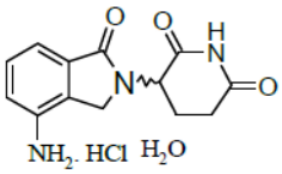

Figure 1: active substance structure

The active substance is a white to yellow coloured solid which is non-hygroscopic, very slightly soluble to practically insoluble in water with the highest solubility in strongly acidic media.

The chemical structure of lenalidomide hydrochloride monohydrate was elucidated and confirmed by a combination of High-Resolution Mass Spectrometry, Mass Spectroscopy, Nuclear Magnetic Resonance Spectroscopy (1H & 13C NMR), Infrared Spectroscopy and UV Spectroscopy. The solid-state properties of the active substance were measured by powder and single-crystal X-ray diffraction and dynamic vapour sorption.

Lenalidomide exhibits stereoisomerism due to the presence of one chiral centre. Lenalidomide hydrochloride monohydrate is produced as a racemic mixture.

Lenalidomide hydrochloride monohydrate exhibits polymorphism. A consistent polymorph is produced.

Manufacture, characterisation and process controls

Detailed information on the manufacturing process of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Lenalidomide is synthesized using well-defined starting materials with acceptable specifications.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

During the procedure, a major objection was raised in relation to the definition of one starting material. In response, the applicant provided detailed justifications. Limits for impurities were tightened and the specification revised with additional tests as requested. The carry-over of impurities from the starting material to the active substance was studied and relevant information included in the ASMF. No impurities formed upstream of the starting material carry-over to the active substance. Therefore, the starting material was deemed acceptable.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

This included a discussion on the limits for potential mutagenic impurities as well as results from spiking experiments. Spiking experiments confirmed the absence of certain potential mutagenic impurities for which it was therefore not necessary to include limits in the active substance specification. The active substance specification includes an appropriate limit for one known mutagenic impurity. The contents of solvents used in the last steps of the manufacturing process of active substance are controlled in the specification of the active substance.

Elemental analysis as per ICH Q3D was performed on three active substance batches. Class 1 and 2A elemental impurities have been considered, including palladium which is intentionally added during the process as a catalyst. Results for all elements are below the 30 % ICH limit and hence no further control of elemental impurities in the active substance is required.

Evaluation of the presence of *N*-nitrosamines in lenalidomide hydrochloride monohydrate shows that the contamination of the *N*-nitrosamine impurities is not expected in the synthesis of the active substance.

The active substance is packaged in a transparent low-density polyethylene bag (LDPE) filled with nitrogen, which comply with Commission Regulation EU No. 10/2011 as amended. These LDPE bags are further packed in another LDPE bag containing a one-gram silica gel pillow pack and the bag is sealed with a strip seal. The bag is then packed in a triple laminated sunlight barrier bag (TSLB) with heat seal and kept in a high-density polyethylene container.

Specification

The active substance specification includes tests for appearance, identity (IR, HPLC), water content (Ph. Eur.), residue on ignition (Ph. Eur.), impurities (Ph. Eur.), assay (Ph. Eur.), residual solvents (Ph. Eur.), microbiological quality (Ph. Eur.) and particle size (Ph. Eur.).

The maximum daily dose for lenalidomide is 25 mg/day. Therefore, the ICH recommended thresholds for reporting, identification and qualification in the active substance are 0.05%, 0.10% and 0.15%, respectively. Impurities limits have been set below the qualification threshold according to ICH Q3A and in line with the TTC according to ICH M7. A TTC limit for one mutagenic impurity has been set in accordance with ICH M7.

In response to a question raised during the assessment, specification limits for particle size were tightened to be not significantly different to the limits of the batches used in the bioequivalence study.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data from three production scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from four production scale batches of active substance from the proposed manufacturer stored in the proposed commercial container closure system for up to 24 months under long term conditions (25ºC / 60% RH), up to 24 months under refrigerated conditions (5ºC) and for up to six months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. No change in relevant specification parameters has been observed.

Photostability testing following ICH guideline Q1B was performed. Results under stressed conditions (acid and base hydrolysis, oxidative degradation, thermal degradation and humidity degradation) were also provided.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period of 36 months when stored under a nitrogen atmosphere at a temperature not exceeding 25°C in the proposed container. Excursions are permitted between 15-30°C.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product is presented as hard capsules containing 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg or 25 mg of lenalidomide. The different hard capsule strengths are appropriately differentiated by their colour and size.

The 2.5 mg and 5 mg strength are weight proportional. In addition, the 7.5 mg is proportional to 10 mg and the 15 mg, 20 mg and 25 mg are weight proportional.

Lenalidomide hydrochloride monohydrate is classified as a BCS I active substance.

Lenalidomide hydrochloride monohydrate exhibits polymorphism. The polymorphic form of the active substance was demonstrated in stability studies and does not change during formulation.

The aim of the product development was to formulate a bioequivalent, effective and safe generic alternative to the reference medicinal product Revlimid hard capsules.

The seven strengths of finished product were designed into three dose-proportional groups with a separate common capsulation mixture for each. One group includes 2.5 mg and 5 mg, the other group includes 7.5 mg and 10 mg and the last group includes 15 mg, 20 mg and 25 mg strength.

The qualitative composition of the excipients is different from that in the reference product.

All the excipients except the empty hypromellose capsule shells are conventional pharmaceutical ingredients and comply with the requirements of the European Pharmacopoeia. The components of empty hypromellose capsule shells comply either with the monograph in Ph. Eur. or with Directive (EU) No. 231/2012 (colourants). Based on the results of ICH stability testing, it has been concluded that the active substance is compatible with the excipients of the present formulations and that the formulation is stable. The test product and the EU reference product exhibit similar impurity profiles. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.2.1 of this report.

The purpose of the development was to choose the same or similar excipients as contained in the reference product. However, compared to the reference product, several modifications of the qualitative composition have been made during the development.

The proposed final formulation showed similar chemical stability compared to the reference product, which confirms good compatibility of active substance with the new excipients. Moreover, compatibility of the active substance with the proposed excipients was additionally verified with ICH stability studies under accelerated and long-term conditions

The information provided to demonstrate the discriminatory power of dissolution method is considered adequate. However, as lenalidomide is a BCS class I active substance with very high solubility over the

physiological pH range and with rapid dissolution, it is not possible to detect any differences in dissolution behaviour.

Clinical bioequivalence studies were performed on the 25 mg and 5 mg capsules. In addition, comparative dissolution profiles of 25 mg and 5 mg capsules of Lenalidomide test product and the reference product were generated in four dissolution media: pH 1.2, pH 4.5, pH 6.8 and in the QC medium. The dissolution profiles can be considered as similar. A strength biowaiver was claimed for the other five strengths not used in clinical bioequivalence studies. All additional five dosage strengths of Lenalidomide capsules (2.5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg) have similar rapid dissolution profiles to the biobatches

The formulations used in the bioequivalence studies were manufactured by the same manufacturer, same manufacturing process and same type of equipment as the to-be marked formulations presented within this marketing authorization application dossier. The production batch size is the same as the size of batches in the bioequivalence study.

The manufacturing process used to produce the generic product is the same as for the reference product (blending and capsules filling). During development, prototypes of each strength were developed and tested in order to develop a final composition of each strength. The critical process parameters determined during development are appropriately controlled during manufacture of the encapsulation mixture.

The primary packaging is peel open, unit dose blister (OPA/Al/PVC//PET/Al). The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of two main steps: manufacturing of the encapsulation mixture and the encapsulation process, followed by packaging.

The process is considered to be a standard manufacturing process.

The critical steps involved in the manufacturing process include preparation of the encapsulation mixture and encapsulation. The in-process controls are adequate for this type of manufacturing process.

Process validation has been carried out on three commercial size batches of each strength. It has been demonstrated that the manufacturing process is capable of producing the finished product of the intended quality in a reproducible manner.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form (appearance, uniformity of dosage units (Ph. Eur.), identification (HPLC, UV), related substances (Ph. Eur.), assay (Ph. Eur.), dissolution (Ph. Eur.) and microbiological purity).

In line with new regulatory requirements, a risk assessment for the presence of nitrosamines has been performed and no risk of nitrosamines presence in the medicinal product was identified.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment and the presented batch data, it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification.

The analytical procedures used in the control of the finished product have been described in a satisfactory manner and validation data of the in-house analytical methods are in accordance with the requirements of the relevant ICH guidelines and acceptable. The information about reference standards is provided and sufficient.

Results of analysis of three production size batches of each strength are within the specification limits at the time of testing, confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

A stability study has been performed on three production scale batches of each strength of the finished product, packed in the proposed market pack in accordance with ICH guidelines. No bracketing and matrixing designs were used in the stability study. Data is available from finished product batches stored for up to 12 months under long term conditions (25±2 °C / 60±5% RH) and up to 6 months under accelerated conditions (40±2 °C / 75±5% RH). Up to 18 months' long-term data is available for the 25 mg capsules. Samples were tested for appearance, assay, degradation products, dissolution and microbiological quality. All results are within the proposed limits. No trend of increasing impurities was observed under accelerated or long-term conditions.

A photostability study was conducted as per ICH Q1B guideline and there were no out of specification results. Therefore, the capsules are not photosensitive.

Based on the results of stability studies under accelerated conditions and the photostability study conducted, no special storage conditions are proposed. The proposed shelf-life of 2 years with no special storage conditions as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

Bioequivalence has been demonstrated between the lenalidomide 5 mg and 25 mg hard capsule and the reference product Revlimid 5 and 25 mg hard capsules and biowaivers have been accepted for the other strengths (2.5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg).

A major objection related to the designation of one of the starting materials was resolved after the applicant provided additional justifications and tightened specification parameters for impurities.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data have been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendation(s) for future quality development

Not applicable.

Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment studies were submitted. This was justified by the applicant as the introduction of Lenalidomide Krka is considered unlikely to result in any significant increase in the combined sales volumes for all lenalidomide containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar.

2.3.3. Discussion on non-clinical aspects

The safety use of hydrochloride monohydrate as the counter ion has been discussed and theirs uses as salt justified. In aqueous solution, the drug substance dissociates to lenalidomide base and chloride ion. Therefore, it is concluded that the drug will possess the same safety and efficacy profile as the originator product in terms of the lenalidomide component.

The applicant's justification for non-submission of an Environmental Risk Assessment is considered acceptable.

The non-clinical data is reflected in the appropriate sections of the SmPC (Sections 4.6 and 5.3). The non-clinical aspects of the SmPC are in line with the SmPC of the reference product (Revlimid capsules SmPC, 2019)

2.3.4. Conclusion on the non-clinical aspects

A summary of the literature with regard to non-clinical data of Lenalidomide Krka and justifications that the different salt of the active substance does not differ significantly in properties with regards to safety and efficacy of the reference product was provided and was accepted by the CHMP. This is in accordance with the relevant guideline and additional non clinical studies were not considered necessary.

Clinical aspects

This is an application for hard capsules containing lenalidomide. To support the marketing authorisation application the applicant conducted 2 bioequivalence studies with cross-over design under fasting conditions. These studies were pivotal for the assessment.

No CHMP scientific advice pertinent to the clinical development was given for this medicinal product.

For the clinical assessment the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **), the Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/09 Rev.1/Corr. 2**) and Lenalidomide product-specific BE guidance (EMA/CHMP/177335/2016/Corr.) in their current versions are of particular relevance.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Exemption

To support this application, the applicant has conducted two bioequivalence studies (study 18-615 and study 19-641) in order to justify an exemption from the requirement to perform bioequivalence studies for the remaining strengths. The BE study on the 5 mg strength was used to support a bio-waiver of the 2.5 mg strength and the study on the 25 mg strength was used to support a biowaiver of the 7.5 mg, 10 mg, 15 mg and 20 mg strengths respectively.

- The applicant requested a waiver of bio-studies on remaining strengths i.e. 7.5/10/15/20 mg, based on the result of the bioequivalence studies conducted with the 5 mg and 25 mg mg strength. The relevant (a)-(f) criteria defined in the applicable bioequivalence guideline were fullfilled by showing either quantitative proportionality between strengths or applying the bracketing approach for quantitatively not proportional strengths.
- Dissolution of lenalidomide hydrochloride monohydrate from Lenalidomide 7.5 mg and 10 mg capsules was compared to lenalidomide base from Revlimid 7.5 mg and 10 mg. Dissolution profiles were performed in four-dissolution medium i.e. 0.1M HCl, acetate buffer pH 4.5, phosphate buffer pH 6.8 and QC medium. Based on the solubility results, the pH-solubility profile of the drug substance indicates that lenalidomide has comparable solubility in both forms – as base and as hydrochloride salt.
- **Absorption Profile**

As per the pharmacokinetics parameter available in the literature, Lenalidomide is rapidly absorbed following oral administration. Following single and multiple doses of REVLIMID in patients with MM the maximum plasma concentrations occurred between 0.5 and 6.0 hours post-dose. The single and multiple dose pharmacokinetic disposition of lenalidomide is linear with AUC and Cmax values increasing proportionally with dose. Multiple dosing at the recommended dose regimen does not result in drug accumulation.

- **Linear pharmacokinetics of lenalidomide**

The pharmacokinetic disposition of lenalidomide is linear for the proposed dosing range (2.5 mg to 25 mg) and there is no accumulation with multiple dosing (Revlimid SPC, 2019).

- **In-vitro Dissolution Data for Biowaiver Request for Different Strengths**

Dissolution profiles of Lenalidomide capsules of additional strengths (2.5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg) were compared to dissolution profiles of Lenalidomide 25 mg capsules and Lenalidomide 5 mg capsules which were used in bioequivalence studies. Dissolution profiles were performed in four different dissolution media without surfactant i.e. 0.1M Hydrochloric acid, Acetate buffer solution pH 4.5, Phosphate buffer solution pH 6.8 and QC medium in order to apply for a biowaiver for additional strengths.

On the basis of the presented dissolution profiles, similarity in dissolution has been demonstrated at the four requested pH levels between the test biobatch (5 mg and 25 mg) and the lower strengths (2.5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg) as more than 85% of the labeled amount of the drug is released within 15 minutes from all strengths of test product and therefore it can be concluded that the dissolution profiles can be considered similar to the test biobatch (5 mg and 25 mg) without further mathematical calculations.

Biowaiver for 2.5 mg, 15 mg and 20 mg strengths

The (a)-(c) criteria defined in the BE guideline are fullfilled since a) the pharmaceutical products are manufactured by the same manufacturing process, b) the qualitative composition of the different strengths is the same and c) the compositions of the strengths are quantitatively proportional. Concerning the criterion (d) (similar in-vitro performance), the applicant has provided comparative dissolution data. Dissolution tests were conducted at different pH values 1.2, 4.5 and 6.8 between 1) the Lenalidomide Krka 2.5 and 5 mg tablets vs bio-batch 5 mg (batch used for the bioequivalence testing) and 2) Lenalidomide Krka 15 and 20 mg vs bio-batch 25 mg (batch used for the bioequivalence testing).

More than 85% of the labeled amount of the drug is released within 15 minutes from all strengths of test product tested in 0.1 N HCl, pH 4.5 Acetate buffer, pH 6.8 Phosphate buffer and QC dissolution medium ~~(0.01M HCl)~~ and thus the dissolution profiles can be considered similar to the test biobatch (5 mg and 25 mg) without further mathematical calculations.

Biowaiver for 7.5 mg and 10 mg strengths

The (a)-(b) criteria defined in the BE guideline are fullfilled since a) the pharmaceutical products are manufactured by the same manufacturing process, b) the qualitative composition of the different strengths is the same. Concedering c) the compositions of the strengths are not quantitatively proportional, the applicant used a bracketing approach.

Concerning the criterion (d) (similar in-vitro performance), the applicant has provided comparative dissolution data. Dissolution tests were conducted at different pH values 1.2, 4.5, 6.8 and QC dissolution medium between 1) the Lenalidomide Krka 7.5 mg and 10 mg tablets vs 5 mg (batch used for the bioequivalence testing) and 2) Lenalidomide Krka 7.5 mg and 10 mg mg vs 25 mg (batch used for the bioequivalence testing). More than 85% of the labeled amount of the drug is released within 15 minutes from both strengths of test product tested in 0.1 N HCl, pH 4.5 Acetate buffer, pH 6.8 Phosphate buffer and the QC dissolution medium and thus the dissolution profiles can be considered similar to the test biobatches (5 mg and 25 mg) without further mathematical calculations.

A) Comparative Dissolution Studies (Test product vs Reference product)

The applicant carried out comparative dissolution studies between the test products (Lenalidomide Krka 5 mg, 7.5 mg, 10 mg, 25 mg capsules, respectively and the reference products (Revlimid 5 mg, 7,5 mg, 10 mg and 25 mg capsules). respectively in four dissolution media i.e. 0.1 M Hydrochloric acid, Acetate buffer solution pH 4.5, Phosphate buffer solution pH 6.8 and QC medium.

Test product (7.5 mg and 10 mg) Vs reference product (7.5 mg and 10 mg)

Based on presented in vitro comparison of dissolution profiles of Lenalidomide 7.5 mg and 10 mg capsules to the corresponding strengths of the reference Revlimid 7.5 mg and 10 mg capsules performed in three different buffers (pH 1.2 , 4.5 and 6.8) and QC dissolution medium , it can be concluded that all batches express similar dissolution profiles in QC medium,0.1M HCl and acetate buffer pH 4.5 as ≥ 85% of lenalidomide is dissolved within 15 minutes.

The exception is slower dissolution profile of lenalidomide from Revlimid 7.5 mg and 10 mg hard capsule in phosphate buffer pH 6.8. According to the applicant, the main reason of slightly slower dissolution of Revlimid 7.5 mg and 10 mg is apparatus type related. Furthermore, different dissolutions profiles between test and reference product is observed at the first time point of 5 minutes.Differences in release at the first time point of 5 minutes between the test and reference products are not found critical, since the observed differences in release more reflect product quality than in vivo performance of lenalidomide as lenalidomide is rapidly absorbed with the tmax of 0.5-2 hours and half-life in plasma of approx. 3-5 hours and possible reasons for the discrepancy is addressed and justified.

Test product (5 mg and 25 mg) Vs reference product (5 mg and 25 mg)

Based on the comparative dissolution profiles of the test product Lenalidomide Krka 5 mg and 25 mg vs the reference product Revlimid 5 mg and 25 mg capsules of "Celgene Europe Limited, UK, in all dissolution media, it can be concluded that all batches express similar dissolution profiles in QC medium and pH 4.5 as ≥ 85% of lenalidomide is dissolved within 15 minutes.

Slower dissolution profile of lenalidomide from Revlimid 5 mg and 25 mg hard capsule in phosphate buffer pH 6.8 is not found critical, since bioequivalence was demonstrated *in vivo* and possible reasons for the discrepancy of the *in vitro/in vivo* data is addressed and justified.

In view of dissolution data, linear pharmacokinetics, a biowaiver is supported for the other strengths applied for, 2.5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg. The bracketing approach for the waiving of additional bioequivalence study on the 7.5 mg and 10 mg strengths is considered acceptable. The results of the bioequivalence studies performed with the 5 mg and 25 mg strengths can be extrapolated to the other strengths of 2.5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg.

Clinical studies

To support the application, the applicant has submitted 2 bioequivalence studies to support the bracketing approach pursued to apply for the strength biowaivers as explained in the exemptions section above.

Table 1 Tabular overview of clinical studies

Table 5.1 Listing of Clinical Studies

Type of Study	Study Identifier	Location of Study Report	Objective of the Study	Study Design; Type of Control	Test Product(s); Dosage Regimen; Rout of Administration	No. of Subjects	Healthy Subjects/ Diagnosis of Patients	Duration of Treatment	Study Status; Type of report
BE	18-615 2019-4618	Section 5.3.1.2.	Demonstration of bioequivalence of test to reference capsule formulations under fasting conditions	Open-label, single-dose, randomized, two-period, two-treatment, two-sequence, crossover 7 days wash-out period fasting conditions	**Test Product:** Lenalidomide 25 mg capsules, hard (B. No.: RA0182) **Reference Product:** Revlimid® 25 mg hard capsules (lenalidomide) (B. No.: A2530AC) One capsule of the test or reference formulation in one period / Oral	70	Healthy male subjects	Single Dose	Complete Full
BE	19-641 2019-4664	Section 5.3.1.2.	Demonstration of bioequivalence of test to reference capsule formulations under fasting conditions	Open-label, single-dose, randomized, two-period, two-treatment, two-sequence, crossover 7 days wash-out period fasting conditions	**Test Product:** Lenalidomide 5 mg capsules, hard (B. No.: RA0222) **Reference Product:** Revlimid® 5 mg hard capsules (lenalidomide) (B. No.: A2642KI) One capsule of the test or reference formulation in one period / Oral	42	Healthy male subjects	Single Dose	Complete Full

Pharmacokinetics

Sponsor Study Number: 18-615

Study Title: A Single-Dose, Bioequivalence Study of Two Formulations of Lenalidomide 25 mg Capsules, Hard under Fasting Conditions.

Methods

Study design

This was an open-label, single-dose, randomized, two-period, two-treatment, two-sequence, crossover, study, designed to evaluate the bioequivalence of lenalidomide in healthy, non-smoking, male subjects under fasted conditions, with a washout period of 7 days between the successive dosing days. In each period, subjects were administered a single, oral dose of the test or reference product, in accordance with the randomization scheme, after an overnight fast of at least 10 hours.

The primary objective of this study was to evaluate the bioequivalence between Lenalidomide 25 mg capsules, hard and Revlimid 25 mg hard capsules (lenalidomide) after a single dose in healthy subjects administered under fasted conditions.

The secondary objective of this study was to evaluate the safety and tolerability of the study treatments.

Summary of study information

The protocol was approved by the institutional review board (IRB), the Ethics Review Board of Optimum Clinical Research Inc. prior to initiating the study.

The study was conducted at the highest/most sensitive strength (i.e., 25 mg for lenalidomide) and under fasting conditions, which reflects recommendations in the reference product's summary of product characteristics for the administration of the product irrespective of mealtimes and it is considered to be the most sensitive condition to detect a potential difference between formulations. Such a study design is in line with the Lenalidomide Product-specific Bioequivalence Guidance (EMA/CHMP/177335/2016/Corr).

The study was initiated with 70 healthy adult male subjects in accordance with the protocol. Each subjects received one tablet of either a single, oral dose of 25 mg (1 × 25 mg) of the test product, lenalidomide capsules, 25 mg or a single oral dose of 25 mg (1 × 25 mg) of the reference product, Revlimid capsules 25 mg randomly with 240 mL of drinking water on the day of dosing as per the randomization schedule under fasting conditions in each period of the study. Dosing occurred following an overnight fast of at least 10 hours. There was a 7-day washout period between dosing times for the two treatment periods, which is considered adequate as lenalidomide has an elimination half-life of 3-5 hours (about 3 hours in the actual study). Pre-dose levels were not observed in any subjects.

In each study period, blood samples were collected within 60 minutes prior to dose administration (0 hour) and at intervals over 14.00 hours after administration of dose. The sampling period was sufficient to characterize the plasma concentration-time profile. Blood sampling points are appropriate to allow an accurate measurement of T_{max}.

The quantification of Lenalidomide in plasma was performed using ultra high-performance liquid chromatography with tandem mass spectroscopy.

Test and reference products

Test product (A): Lenalidomide 25 mg capsules, hard (as lenalidomide hydrochloride monohydrate)	**Reference product (B): Revlimid® 25 mg capsules, hard (as lenalidomide)**
Batch No.: RA0182 Measured content (% of label claim): 100, 9% Manufactured date: 11 December 2018 Re-test date: 11 March 2019 Release date: 21 December 2018 (according to certificate of analysis)	Batch No.: A2530AC Measured content (% of label claim): 100, 1% Exp. Date: January 2020

Revlimid 25 mg hard capsules is an immediate release tablet formulation containing lenalidomide, which was approved in Europa on 14 June 2007, through a centralised marketing authorization procedure under Article 8.3 of Directive 2001/83/EC. Therefore, the choice of the reference medicinal product is acceptable. The member state where the reference product was purchased from is Denmark, EU.

Satisfactory certificates of analysis of the test and reference products bio-batch are presented. Assay of the test and reference product is 100, 9% and 100, 1%, respectively. The difference in the assay

between the test and reference product is less than 5%, which is acceptable. This difference was not taken into account in the pharmacokinetic or statistical analysis.

The test product used in the study was considered to be representative of the product to be marketed.A signed statement confirming that the test product has the same quantitative composition and is manufactured by the same process as the one submitted for authorisation is provided.

Population(s) studied

As per the protocol, 70 non-smoker, healthy, adult, male volunteers 18 to 55 years of age, having a Body Mass Index (BMI) between ≥19.0 and ≤30.0 kg/m2 and with normal clinical and laboratory results. The population chosen was according to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1). Inclusion and exclusion criteria were acceptable and performed according to the protocol requirements. All the subjects were dosed as per the randomization.

The sample size calculation provided by the applicant is considered acceptable.

Out of the dosed 70 subjects, 67 subjects completed the study. Three subjects discontinued, after enrolment in the study in Period-I. The reason of the withdrawal was acceptable. In response to the D120 LoQ, the applicant has documented withdrawal of those subjects by presenting the Case Report Forms (CRFs).

A total of 67 subjects were included in the pharmacokinetic and statistical analysis. The safety assessment includes information for all 70 subjects who were dosed at least once during this study.

There were no protocol deviations during the conduct of study except minor sampling time point deviations (up to 5 minutes). Actual time-points of the sample collection are used for the calculation of pharmacokinetic parameters.

Analytical methods

Pre-study and in-study validations were performed according to the requirements of the EMA Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/09).

Statement on GLP compliance is provided.

In-study validation (study 18-615):

The sample analysis was performed according to Bioanalytical Sample Analysis Plan.

The plasma samples of subjects were analysed using a validated achiral, liquid chromatographic tandem mass spectrometric detection (LC-MS/MS) method.

Check-in plasma samples from tentative subjects were assayed between March 6, 2019 and March 7, 2019. Plasma samples from dosed subjects were assayed between March 8, 2019 and March 19, 2019.

All personnel from the Bioanalytical Facility were blinded regarding the study randomization code and treatment plan.

Long-term storage stability was established.Certificates of analysis for reference and internal standard were included in the dossier.

Details of subject samples:

Clinical Facility. 140 check-in plasma samples from 70 tentative subjects, 6 unused samples from tentative subjects, who were not enrolled in the study, and plasma samples from 70 dosed subjects were

received at bioanalytical site. During transfer to the bioanalytical centre, the samples were kept in a box containing adequate amount of dry ice. All the received samples were transferred to the freezer at the bioanalytical facility.

Calibration curve standards and quality control samples met the acceptance criteria for all the runs used for the final data, demonstrating satisfactory performance of the method during the analysis of study subject samples.

Repeat samples

Seven (7) plasma samples were repeated in accordance with applicable SOPs due to unacceptable internal standard response, poor chromatography and sample position error. In response to the D120 LoQ, the applicant has clarified the raised issue regarding reanalysis of samples due to sample position error in the autosampler rack. The reasons for reanalysis of samples are thus considered justified.

Incurred Sample Reanalysis (ISR)

ISR was performed with more than 5 % of the samples as requested by the guideline for total number samples exceeding 1000 samples. The ISR assay complied with the acceptance criteria as all samples (100%) were within the acceptance criteria (±20%) indicating that the analysis is robust.

Twenty percent of the subject's chromatograms are presented in this report.

Pre-study validation (study 18-615):

Two validations were performed, because the original version of the validation report was re-formatted to comply with the current SOP requirements and procedures for eCTD submission.

A liquid chromatographic tandem mass spectrometric method for the determination of lenalidomide in human plasma has been developed and validated according to Bioanalytical Validation Plan.

Adequate Certificates of analysis of the analyte and the internal standard are provided for each version of the Method validation report.

The method validation report provides results of calibration curve standard, quality control sample data, sensitivity (precision and accuracy), linearity, stability data, recovery, dilution integrity, selectivity, injection carryover, matrix effect, matrix factor, hemolyzed QC samples experiment, lipemic QC samples experiment, specificity, evaluation of Lenalidomide in the presence of concomitant medications and hormonal contraceptives, and batch size determination. The method met the acceptance criteria for all the validation parameters evaluated, demonstrating acceptable performance. It can be concluded that the quantification method is selective for the analysis of Lenalidomide in presence of the co-administered drugs. The co-administered drug did not affect the determination of Lenalidomide or IS.

In addition, no significant degradation of Lenalidomide was observed under different storage conditions.

The possible back conversion of metabolites to Lenalidomide was evaluated at the stage of bioanalytical method validation. It can be concluded that there was no back-conversion.

It was demonstrated that the method has acceptable selectivity and specificity and is able to accurately quantify concentrations of lenalidomide in human plasma.

Pharmacokinetic variables

The PK parameters C_{max}, AUC_t, $AUCi_{nf}$, T_{max}, K_{el}, and T_{half} estimated for lenalidomide were computed using a noncompartmental approach in Phoenix™ WinNonlin (version 8.1).

Primary pharmacokinetic parameters:

C_{max} and AUC_t

Secondary pharmacokinetic parameters:

$AUC_{inf,}$ T_{max}, K_{el}, and T_{half}

The selected primary pharmacokinetic variables are appropriate for a single dose bioequivalence study and in line with the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1).

Pharmacokinetic software and method for PK parameters estimation are considered acceptable.

Actual time of blood collection was considered for pharmacokinetic calculations.

Statistical methods

Descriptive statistics for the PK parameters of lenalidomide were calculated and included number of observations, arithmetic mean, standard deviation (SD), geometric mean (where applicable), coefficient of variation (CV), median, minimum, and maximum.

The comparison of the pharmacokinetic parameters was carried out using PROC GLM procedure from SAS® (version 9.4).

The ln-transformed pharmacokinetic parameters AUC_t, $AUCi_{nf}$ and C_{max} parameters were subjected to Analysis of Variance (ANOVA) for lenalidomide. The significance of the sequence, period, treatment, and subject (sequence) effects (all fixed) was tested. All the effects were tested at the 5% level of significance.

Using the same statistical model, the least-squares-means (LSMs), the differences between the treatments LSMs, and the corresponding standard errors of these differences were estimated for log-transformed AUC_t, AUC_{inf}, and C_{max} parameters.

Based on log-transformed data, ratios of the geometric means for treatments and the corresponding 90% confidence intervals (CIs) were calculated for AUC_t and C_{max}.

The statistics are described adequately, and the methods are acceptable. The criteria for concluding bioequivalence for lenalidomide was adequate. Protocol deviations/violations were not reported with regards the statistical analysis of the study.

Results

The pharmacokinetic parameters of Lenalidomide for Test Product-T and Reference Product-R are summarized in the following tables:

Table 2 Pharmacokinetic parameters for lenalidomide (non-transformed values)

	Test		**Reference**	
	arithmetic geometric mean	**SD CV%**	**arithmetic geometric mean**	**SD CV%**
AUC(0-t) (ng*hr/ml)	1613.31 1587.45	277.07 17.21	1542.17 1523.12	245.73 15.93

	Test		Reference	
	arithmetic geometric mean	**SD CV%**	**arithmetic geometric mean**	**SD CV%**
$AUC_{(0-\infty)}$ (ng*hr/ml)	1676.72 1651.46	296.98 17.71	1608.98 1587.59	266.03 16.53
C_{max} (ng/ml)	470.43 454.17	125.92 26.77	422.60 411.81	97.52 23.08
T_{max}*(h)	1.18 1.10 1.00, (0.5, 2.50) *	0.47 0.40	1.04 0.98 1.00, (0.5, 2.50) *	0.40 38.68
AUC_{0-t} area under the plasma concentration-time curve from time zero to 14 hours> $AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity C_{max} maximum plasma concentration T_{max} time for maximum concentration (* median, range)				

Table 3 Statistical analysis for lenalidomide (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
$AUC_{(0-t)}$ **(ng*hr/ml)**	1.04	102.65-105.91	5
C_{max} **(ng/ml)**	1.10	104.99-115.94	17
* estimated from the Residual Mean Squares			

Mean plasma concentration vs. time profiles (semi-log and linear) of Lenalidomide 25 mg test and reference products under fasting conditions are depicted in figure below (N=67).

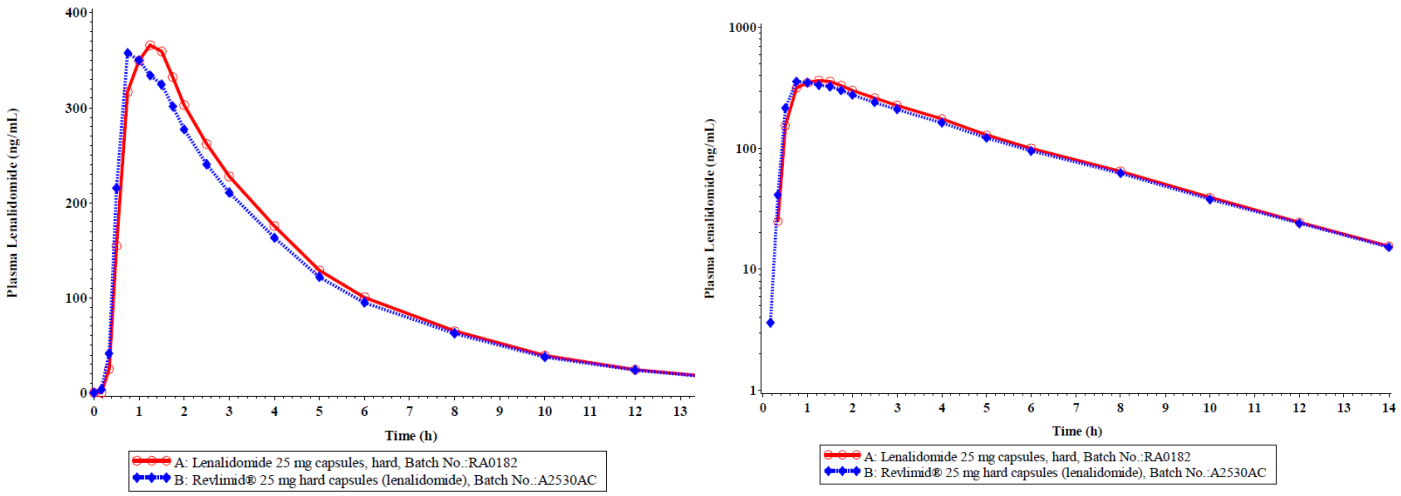

Figure 2 ***Mean Plasma Concentrations time profile (****Linear and Semi Log Plot)*

Based on the individual time-concentration curves, the absorption phase is well covered by the sampling scheme up to 14 hours. T_{max} was not observed in any of the subjects in the first sample time point. No pre-dose concentration has been detected.

Based on the statistical analysis submitted by the applicant the test product is equivalent to the reference with respect to the extent and rate of absorption/exposure as the 90% confidence intervals for the ln-transformed C_{max} and AUC_t are within the acceptance range of 80.00 – 120.00%.

The extrapolated AUC is not higher than 20% for any single subject.

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The individual plasma time-concentration curves for each subject have been presented.

In conclusion, bioequivalence with respect to the rate and extent of absorption of lenalidomide has been shown for the 25 mg strength between test and reference product under fasting condition.

Safety data

Ten (10) subjects reported 15 AEs. Five (5) subjects receiving treatment A reported 6 AEs, and 5 subjects receiving treatment B reported 9 AEs. Of these, 9 AEs affecting 6 subjects were deemed to be possibly related to the study drugs.

The most prevalent treatment related AEs were headache (2 events affecting 2 subjects and somnolence (2 events affecting 2 subjects). One (1) subject reported one episode of diarrhoea approximately 2 hours following treatment A dosing.

All AEs were mild in severity and resolved prior to the end of the study. No SAEs were reported during the conduct of this study. None of the AEs had a significant impact on the safety of the subjects or on the integrity of the study results.

There were no clinically significant changes in the clinical laboratory measurements over the course of the study which could be reasonably associated with the formulations under investigation.

Data from this study demonstrated that the test and the reference products were well tolerated by healthy subjects, as a single dose (1 x 25 mg capsule) administration. None of the AEs had a significant impact on the safety of the subjects. No new safety concerns related to the administered formulations were noted during the conduct of the study.

Sponsor Study Number: 19-641 Study title: *A Single-Dose, Bioequivalence Study of Two Formulations of Lenalidomide 5 mg Capsules, Hard under Fasting Conditions.*

Methods

Study design

This was an open-label, single-dose, randomized, two-period, two-treatment, two-sequence, crossover, study, designed to evaluate the bioequivalence of lenalidomide in healthy, non-smoking, male subjects under fasted conditions, with a washout period of 7 days between the successive dosing days. In each period, subjects were administered a single, oral dose of the test or reference product, in accordance with the randomization scheme, after an overnight fast of at least 10 hours.

The primary objective of this study was to evaluate the bioequivalence between Lenalidomide 5 mg capsules, hard and Revlimid 5 mg hard capsules (lenalidomide) after a single dose in healthy subjects administered under fasted conditions.

The secondary objective of this study was to evaluate the safety and tolerability of the study treatments.

Summary of study information

The protocol was approved by the institutional review board (IRB), the Ethics Review Board of Optimum Clinical Research Inc. prior to initiating the study.

The study was conducted at the second lowest strength (i.e., 5 mg for lenalidomide) and under fasting conditions, which reflects recommendations in the reference product's summary of product characteristics for the administration of the product irrespective of mealtimes. Such a study design is in line with the Lenalidomide Product-specific Bioequivalence Guidance EMA/CHMP/177335/2016/Corr).

The study was initiated with 42 healthy adult male subjects in accordance with the protocol. Each subjects received one tablet of either a single, oral dose of 5 mg (1 × 5 mg) of the test product, lenalidomide capsules, 5 mg or a single oral dose of 5 mg (1 × 5 mg) of the reference product, Revlimid capsules 5 mg randomly with 240 mL of drinking water on the day of dosing as per the randomization schedule under fasting conditions in each period of the study. Dosing occurred following an overnight fast of at least 10 hours. There was a 7-day washout period between dosing times for the two treatment periods, which is considered adequate as lenalidomide has an elimination half-life of 3-5 hours (about 3 hours in the actual study). Pre-dose levels were not observed in any subjects.

In each study period, blood samples were collected within 60 minutes prior to dose administration (0 hour) and at intervals over 14.00 hours after administration of dose, totalling 19 samples in each period. The sampling period was sufficient to characterize the plasma concentration-time profile. Blood sampling points are appropriate to allow an accurate measurement of T_{max}.

The quantification of Lenalidomide in plasma was performed using ultra high-performance liquid chromatography with tandem mass spectroscopy.

Test and reference products

Test product (A): Lenalidomide 5 mg capsules, hard (as lenalidomide hydrochloride monohydrate)	**Reference product (B):Revlimid® 5 mg capsules, hard (as lenalidomide)**
Batch No.: RA0222 Measured content (% of label claim): 101, 2% Manufactured date: 19 April 2019 Re-test date: 19 July 2019 Release date: (according to certificate of analysis)	Batch No.: A2642KI Measured content (% of label claim): 98, 7% Exp. Date: June 2020

Revlimid 5 mg hard capsules is an immediate release tablet formulation containing lenalidomide, which was approved in Europa on 14 June 2007, through a centralised marketing authorization procedure under Article 8.3 of Directive 2001/83/EC. Therefore, the choice of the reference medicinal product is acceptable. The member state where the reference product was purchased from is Denmark, EU.

Satisfactory certificates of analysis of the test and reference products bio-batch are presented. Assay of the test and reference product is 101, 2% and 98, 7%, respectively. The difference in the assay between

the test and reference product is less than 5%, which is acceptable. This difference was not taken into account in the pharmacokinetic or statistical analysis.

Size of the test product bio-batch capsules was assessed and found acceptable. A signed statement confirming that the test product has the same quantitative composition and is manufactured by the same process as the one submitted for authorisation is provided.

Population(s) studied

As per the protocol, 42 non-smoker, healthy, adult, male volunteers 18 to 55 years of age, having a Body Mass Index (BMI) between ≥19.0 and ≤30.0 kg/m2 and with normal clinical and laboratory results. The population chosen was according to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1). Inclusion and exclusion criteria were acceptable and performed according to the protocol requirements. All the subjects were dosed as per the randomization.

Out of the dosed 42 subjects, 39 subjects completed the study. Three subjects discontinued during period 1 or at period 2 check-in. The reason of the withdrawal was acceptable. In response to the D120 LoQ, the applicant has documented withdrawal of those subjects by presenting the Case Report Forms (CRFs).

A total of 39 subjects were included in the pharmacokinetic and statistical analysis. The safety assessment includes information for all 42 subjects who were dosed at least once during this study.

Analytical methods

Pre-study and in-study validations were performed according to the requirements of the EMA Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/09).

Statement on GLP compliance is provided.

In-study validation (study 19-641)

The sample analysis was performed according to Bioanalytical Sample Analysis Plan.

The plasma samples of subjects were analysed using a validated achiral, liquid chromatographic tandem mass spectrometric detection (LC-MS/MS) method. The method involved a liquid-liquid extraction. Certificates of analysis for reference and internal standard were included in the dossier.

All personnel from the Bioanalytical Facility were blinded regarding the study randomization code and treatment plan.

Long-term storage stability was established

Details of subject samples:

96 check-in plasma samples from 48 tentative subjects, and plasma samples from 42 dosed subjects. During transfer to the bioanalytical centre, the samples were kept in a box containing adequate amount of dry ice. All the received samples were transferred to the freezer at the bioanalytical facility.

Calibration curve standards and quality control samples met the acceptance criteria for all the runs used for the final data, demonstrating satisfactory performance of the method during the analysis of study subject samples.

Repeat samples
One subject sample from was repeated to confirm the presence of peak in the pre-dose sample in accordance with SOP LAB105.14.

Incurred Sample Reanalysis (ISR)
One hundred and thirty one (131) study samples, were re-assayed as ISR. ISR was performed with more than 5 % of the samples as requested by the guideline for total number samples exceeding 1000 samples. The ISR assay complied with the acceptance criteria as all samples (100%) were within the acceptance criteria (±20%) indicating that the analysis is robust.

Twenty percent of the subject's chromatograms are presented in this report.

Pre-study validation (study 19-641)

A liquid chromatographic tandem mass spectrometric detection (LC-MS/MS) method for the determination of lenalidomide in human plasma has been developed and validated. The method involved a liquid-liquid extraction. Adequate Certificates of analysis of the analyte and the internal standard are provided for each version of the Method validation report.

The method validation report provides results pertaining to selectivity, matrix effect, matrix factor, hemolyzed and lipemic plasma experiments, specificity (concomitant medication and hormonal contraceptives interference), injection carryover, recovery, intra and inter-day precision and accuracy, dilution integrity, linearity, stability, evaluation in the presence of concomitant medications and hormonal contraceptives as well as batch size determination. The method met the acceptance criteria for all the validation parameters evaluated, demonstrating acceptable performance. In addition, no significant degradation of Lenalidomide was observed under different storage conditions.

The LLOQ was sensitive enough to detect levels of 5% of the minimum C_{max} to exclude the possibility of a relevant carry-over effect.

The co-administered drugs and hormonal contraceptives did not show any significant interference. It can be concluded that the quantification method is selective for the analysis of Lenalidomide in presence of the above mentioned co-administered drugs and hormonal contraceptives.

The possible back conversion of metabolites to Lenalidomide was evaluated at the stage of bioanalytical method validation. It can be concluded that there was no back-conversion.

It was demonstrated that the method has acceptable selectivity and specificity and is able to accurately quantify concentrations of Lenalidomide in human plasma.

The long-term stability data of Lenalidomide stored human plasma at -25°C ± 10°C was demonstrated.

Pharmacokinetic variables

The PK parameters C_{max}, AUC_t, AUC_{inf}, T_{max}, K_{el}, and T_{half} estimated for lenalidomide were computed using a noncompartmental approach in Phoenix™ WinNonlin® (version 8.1).

Primary pharmacokinetic parameters:

C_{max}, AUC_{0-t} and $AUC_{0-\infty}$

Secondary pharmacokinetic parameters:

T_{max}, K_{el}, and T_{half}

The PK parameters/observations estimated for lenalidomide using a noncompartmental approach in Phoenix™ WinNonlin (version 8.1).

The selected primary pharmacokinetic variables are appropriate for a single dose bioequivalence study and in line with the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1).

Pharmacokinetic software and method for PK parameters estimation are considered acceptable.

Actual time of blood collection was considered for pharmacokinetic calculations.

Statistical methods

Descriptive statistics for the PK parameters of lenalidomide were calculated and included number of observations, arithmetic mean, standard deviation (SD), geometric mean (where applicable), coefficient of variation (CV), median, minimum, and maximum.

The comparison of the pharmacokinetic parameters was carried out using PROC GLM procedure from SAS® (version 9.4).

The ln-transformed pharmacokinetic parameters AUC_t, AUC_{inf}, and C_{max} parameters were subjected to Analysis of Variance (ANOVA) for lenalidomide. The significance of the sequence, period, treatment, and subject (sequence) effects (all fixed) was tested. All the effects were tested at the 5% level of significance.

Using the same statistical model, the least-squares-means (LSMs), the differences between the treatments LSMs, and the corresponding standard errors of these differences were estimated for log-transformed AUC_t, AUC_{inf}, and C_{max} parameters.

Based on log-transformed data, ratios of the geometric means for treatments and the corresponding 90% confidence intervals (CIs) were calculated for AUC_t, AUC_{inf}, and C_{max}.

The statistics are described adequately, and the methods are acceptable. The criteria for concluding bioequivalence for lenalidomide was adequate. Protocol deviations/violations were not reported with regards the statistical analysis of the study.

Results

Table 4 Pharmacokinetic parameters for lenalidomide (non-transformed values)

	Test		**Reference**	
	arithmetic geometric mean	**SD CV%**	**arithmetic geometric mean**	**SD CV%**
$AUC_{(0-t)}$ **(ng*hr/ml)**	302.42 297.93	54.93 18.16	296.25 292.73	48.06 16.22
$AUC_{(0-\infty)}$ **(ng*hr/ml)**	318.06 312.61	63.78 20.05	310.97 306.73	54.76 17.61
C_{max} (ng//ml)	89.48 87.53	19.51 21.81	89.06 87.52	16.89 18.97
T_{max}*(h)	1.00 0.95 0.75, (0.50-1.75) *	0.34 33.47	0.83 0.79 0.75, (0.50-2.00) *	0.33 39.74
AUC_{0-t} area under the plasma concentration-time curve from time zero to 14 hours> $AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity C_{max} maximum plasma concentration T_{max} time for maximum concentration (* median, range)				

Table 5 Statistical analysis for lenalidomide (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
$AUC_{(0-t)}$ **(ng*hr/ml)**	1.02	99.86-103.95	5
C_{max} **(ng/ml)**	1.00	99.97-106.22	16
* estimated from the Residual Mean Squares			

Mean plasma concentration vs. time profiles (semi-log and linear) of Lenalidomide 5 mg test and reference products under fasting conditions are depicted in figure below.

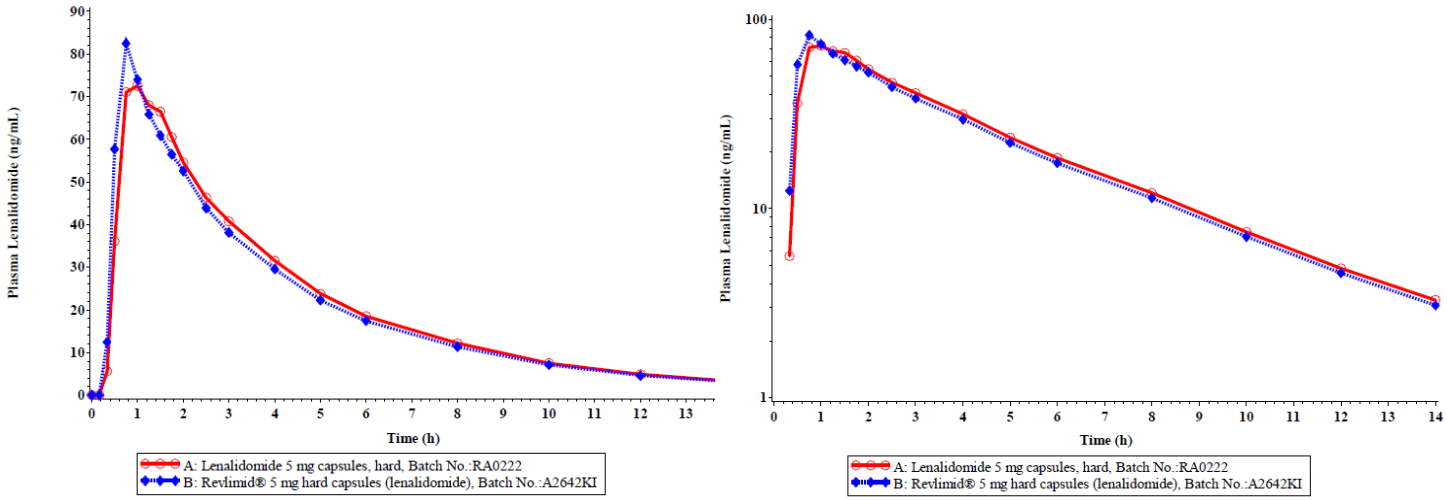

Figure 3 ***Mean Plasma Concentrations time profile (****Linear and Semi Log Plot)*

T_{max} was not observed in any of the subjects in the first sample time point. No pre-dose concentration has been detected.

The extrapolated AUC is not higher than 20% for any single subject.

No subject received concomitant medication during this study. The subject No. received medication after he withdrawn from the study.

Based on the statistical analysis submitted by the applicant the test product is equivalent to the reference with respect to the extent and rate of absorption/exposure as the 90% confidence intervals for the ln-transformed C_{max}, $AUC_{0-\infty}$ and AUC_{0-t} are within the acceptance range of 80.00 – 120.00%.

In conclusion, bioequivalence with respect to the rate and extent of absorption of lenalidomide has been shown for the 5 mg strength between test and reference product under fasting condition.

Safety data

No SAEs were reported during the conduct of this study.

Six (6) subjects reported a total of 6 TEAEs, all of which were considered mild in severity and resolved by the end of the study without intervention. One (1) subject receiving treatment A reported hypotension in period 1, and 5 subjects receiving treatment B reported 5 TEAEs. Of these, 4 TEAEs affecting 4 subjects were deemed to be possibly related to the study drugs.

One (1) subject was dismissed from the study due to a TEAE (neutrophil count decreased) which was mild in severity, possibly related to the IMP, and resolved upon repeated measurement.

None of the AEs had a significant impact on the safety of the subjects or on the integrity of the study results

There were no serious AEs during the conduct of the study. Data from this study demonstrated that the test and the reference products were well tolerated by healthy subjects, as a single dose (1 x 5 mg capsule) administered administration. None of the AEs had a significant impact on the safety of the subjects. No new safety concerns related to the administered formulations were noted during the conduct of the study.

Conclusions

Based on the presented bioequivalence studies Lenalidomide Krka is considered bioequivalent with Revlimid.

The results of studies 18-615 and 19-641 with 25 mg and 5 mg formulations can be extrapolated to other strengths 2.5, 7.5, 10, 15, 20 mg using the bracketing approach according to conditions in the Guidelines.

Pharmacodynamics

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

Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

Discussion on clinical aspects

This application concerns a centralised procedure for the Lenalidomide Krka 2.5mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg & 25 mg hard capsules with *lenalidomide hydrochloride monohydrate* as active substance. Essential similarity is claimed to Revlimid 2.5mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg & 25 mg hard capsules containing *lenalidomide base*, Celgene Europe BV approved via centralised procedure on 14 June 2007 (MAA No: EU/1/07/391/001-014).

Lenalidomide is a well-known active substance with established efficacy and tolerability.

A clinical overview has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional clinical data.

To support this application, the applicant has conducted two bioequivalence studies (study 18-615 and study 19-641) in 2019, one with 5 mg strength and one with the 25 mg strength. The 25 mg strength is listed in the EMA Product-specific Guidance for Lenalidomide (EMA/CHMP/177335/2016/Corr.) as being the highest strength to be used for a drug with linear pharmacokinetics with limited information on solubility available.

For the other strengths (2.5 mg, 5 mg, 10 mg, 15 mg and 20 mg), the applicant requested a bio-waiver according to lenalidomide product-specific guidance (EMA/CHMP/177335/2016/Corr.), which is acceptable as all biowaiver criteria were fulfilled.

In addition, the applicant used a bracketing approach for the waiving of additional bioequivalence studies on the 7.5 mg and 10 mg strengths as the compositions of both strengths is not quantitatively proportional in composition to other strengths (2.5 mg, 5 mg, 15 mg, 20 mg and 25 mg). This approach is in accordance with the requirements stated in the Guideline on the investigation of bioequivalence. As two bioequivalence studies with 5 mg and 25 mg strengths are considered the extremes, the bracketing approach for the waiving of additional bioequivalence study on the 7.5 mg and 10 mg strengths is considered valid in this situation.

Both studies (study 18-615 and study 19-641) were designed as randomized, open-label, single-dose, two-period, two-treatment, two-sequence, crossover study to evaluate the bioequivalence of the test Lenalidomide Krka 5 mg and 25 mg hard capsule (containing 5 mg and 25 mg of Lenalidomide hydrochloride monohydrate) with the reference Revlimid 5 mg and 25 mg hard capsule (containing 5 mg and 25 mg of Lenalidomide) of Celgene Europe Limited, in healthy, adult, non-smoking, male subjects under fasted conditions, with a washout period of 7 days between the successive dosing days.

The study design, study population, selection of PK parameters, determination of sample size, statistical evaluation of the PK parameters as well as the acceptance ranges for bioequivalence are in accordance with the requirements of the Lenalidomide product-specific bioequivalence guidance (EMA/CHMP/177335/2016) and with the bioequivalence guideline (CPMP/EWP/QWP/1401/98 Rev.1 Cor**). Withdrawal of subjects in both studies was documented by presenting the Case Report Forms (CRF) of these subjects.

The choice of the reference product in both studies (study 18-615 and study 19-641) has been justified.

The Analytical method (liquid chromatographic tandem mass spectrometric method) used for the determination of lenalidomide in human plasma for both studies (study 18-615 and study 19-641) has been adequately validated. Pre-study and in-study validations were performed according to the requirements of the EMA Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/09).

The pharmacokinetic parameters C_{max}, AUC_t, AUC_{inf} (primary pharmacokinetic parameters) as well as T_{max}, K_{el}, T_{half} (secondary pharmacokinetic parameters) estimated for lenalidomide for both studies (study 18-615 and study 19-641) were computed using a noncompartmental approach in Phoenix™ WinNonlin (version 8.1).

The comparison of the pharmacokinetic parameters for both studies (study 18-615 and study 19-641) was carried out using PROC GLM procedure from SAS (version 9.4).

The ln-transformed pharmacokinetic parameters AUC_t, $AUCi_{nf}$, and C_{max} parameters were subjected to Analysis of Variance (ANOVA) for lenalidomide. The significance of the sequence, period, treatment, and subject (sequence) effects (all fixed) was tested. All the effects were tested at the 5% level of significance.

The results of study 18-615 showed that the ratios of the geometric least square mean of ln-transformed data (test/reference) for AUC_{tnf} and C_{max} were within the acceptable BE range (80.00%-125.00%). The absence of ANOVA analysis for AUC_{inf} of lenalidomide is acceptable.

The results of study 19-641 showed that the ratios of the geometric least square mean of ln-transformed data (test/reference) for AUC_t, AUC_{inf} and C_{max} were within the acceptable BE range (80.00%-125.00%).

For study 18-615, a significant subject (sequence) and treatment effects have been detected for AUC_t, AUC_{inf} and C_{max}. The applicant has not provided any discussion concerning the statistical significance of formulation/treatment and subject (sequence) effects shown in the relevant ANOVA tables. However, significance of these factors is irrelevant, no question is raised.

Safety evaluation performed for both studies (study 18-615 and study 19-641) demonstrated that the test and the reference products were well tolerated by healthy subjects, as a single dose (1 x 5 mg capsule) or (1 x 25 mg capsule) administration. None of the AEs had a significant impact on the safety of the subjects. No new safety concerns related to the administered formulations were noted during the conduct of the study.

Biowaiver of Strengths

In view of dissolution data, linear pharmacokinetics, a biowaiver is supported for the other strengths applied for, 2.5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg. The conclusion of the bioequivalence studies (study 18-616 and study 19-641) with the Lenalidomide Krka 5 mg and 25 mg strengths can be extrapolated to the lower strengths of 2.5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg.

Conclusions on clinical aspects

A summary of the literature with regard to clinical data of Lenalidomide Krka and justifications that the different salt of the active substance does not differ significantly in properties with regards to safety and efficacy of the reference product was provided and was accepted by the CHMP. This is in accordance with the relevant guideline and additional clinical studies were considered necessary.

Based on the results obtained in the bioequivalence studies (study 18-616 and study 19-641)the Lenalidomide 5 mg and 25 mg strengths can be considered bioequivalent with the originator product Revlimid 5 mg and 25 mg strengths (Celgene Europe Limited, UK), respectively.

As those two bioequivalence studies with 5 mg and 25 mg strengths are considered the extremes, the bracketing approach for the waiving of additional bioequivalence study on the 7.5 mg and 10 mg strengths is considered acceptable. The results of the study 18-615 with the 25 mg strength can be extrapolated to the strengths 7.5 mg, 10 mg, 15 mg and 20 and the results of study 19-641 with the 5 mg strength can be extrapolated to the strengths 2.5 mg, as the biowaiver of additional strength criteria are fulfilled according to the requirements specified in section 4.1.6 of the Guideline on the investigation of bioequivalence.

Risk management plan

Safety concerns

Table 6 Summary of the safety concerns

Summary of safety concerns	
Important identified risks	• Teratogenicity • Serious Infection due to Neutropenia • Secondary primary malignancies • *For FL (follicular lymphoma):* TFR
Important potential risks	• Cardiac failure • Cardiac arrhythmias • Ischaemic heart disease (including myocardial infarction)

Summary of safety concerns	
	• Off-label use
Missing information	• None

Pharmacovigilance plan

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for the following safety concerns:	Follow-up Form Title
Teratogenicity	Event-Specific Questionnaire for HCP - Pregnancy Background (Patient or Partner of Patient) Event-Specific Questionnaire for Patient or Male Patient of Pregnant Partner - Pregnancy Background Event-Specific Questionnaire for HCP - Pregnancy Follow-up (Patient or Partner of Patient) Event-Specific Questionnaire for HCP - Pregnancy Outcome (Patient or Partner of Patient) Event-Specific Questionnaire for Patient or Male Patient of Pregnant Partner - Pregnancy Outcome Event-Specific Questionnaire for Primary Care Physician or Pediatrician - Infant Follow-up
Serious Infection due to Neutropenia	Neutropenia
Secondary Primary Malignancies	Secondary Primary Malignancies
For MCL (mantle cell lymphoma) or FL (follicular lymphoma): TFR	Tumour flare reaction
Cardiac failure	Cardiac failure
Cardiac arrhythmias	Cardiac arrhythmia and ECG Changes
Ischaemic heart disease (including myocardial infarction)	Myocardial infarction

Summary table of additional pharmacovigilance activities:

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
Monitoring of Pregnancy prevention programme implementation (category 3 study) Status: Planned	Monitoring of implementation and the effectiveness of ppp	*Teratogenicity*	Routine PSURs in line with DLP of the latest EURD list	Data will be reviewed on an on-going basis as a part of signal detection and reported within PSURs with in-line with EURD list

Risk minimisation measures

Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Teratogenicity	**Routine risk minimisation measures:** Section 4.3 of SmPC: contraindicated in pregnant women and in women with childbearing potential unless all the conditions of the lenalidomide Pregnancy Prevention Programme are met. Section 4.4 of SmPC: warnings and precautions for use - Criteria for women of non-childbearing potential - Counselling - Contraception - Pregnancy testing - Precautions for men - Additional precuations - Reference to educational materials, prescribing and dispensing restrictions. Sections 4.6 of SmPC: fertility, pregnancy and lactation Sections 4.8 and 5.3 of SmPC: the	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse reaction follow-up questionnaires for risk of "teratogenicity". **Additional pharmacovigilance activities:** Additional monitoring of implementation of PPP on a country specific basis in accordance with local legal framework and with agreement of the relevant NCA.
	potential teratogenic effects of lenalidomide are highlighted Pack size The pack is based on a 4-week supply of capsules to ensure that woman with childbearing potential are required to obtain a new monthly prescription with a medically supervised pregnancy test. Legal status: Lenalidomide is subject to restricted medical prescription.	

	Additional risk minimisation measures: - Lenalidomide Pregnancy Prevention Programme - Educational programme for healthcare professionals and patients: o HCP kit, o Treatment algorithm, pregnancy reporting form, patient card, patient guide and checklists - Therapy management o Criteria for determining FCBP, Contraceptive measures and pregnancy testing for FCBP o Advice in SmPC and educational materials - System to ensure appropriate measures have been completed - Patient card to document childbearing status, counselling and pregnancy testing	
Serious Infection due to Neutropenia	**Routine risk minimisation measures:** Section 4.2 of SmPC: dose reduction advice for neutropenia. Section 4.4 of SmPC: warning for neutropenia, and infection with or without neutropenia, and advice for	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse reaction follow-up questionnaires for risk of "serious infection due to neutropenia"

	monitoring patients, including blood testing for neutropenia. Advice that patients should report febrile episode promptly. Advice that HBV status should be established before initiating treatment with lenalidomide and advice to exercise caution when lenalidomide is used in patients previously infected with HBV. In addition, advice that the patients should be closely monitored for signs and symptoms of active HBV infection throughout therapy. Section 4.8 of SmPC: listed as ADRs Advice to the doctor to check if patient has ever had hepatitis B infection prior to lenalidomide treatment. **Additional risk minimisation measures:** None.	**Additional pharmacovigilance activities:** None
Secondary primary malignancies	**Routine risk minimisation measures:** Section 4.4 of SmPC warning of secondary primary malignancies and advice for cancer screening Listed as ADRs in Section 4.8 of SmPC. Advice to patients provided in PL **Additional risk minimisation measures:** Educational information for healthcare professionals	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse reaction follow-up questionnaires for risk of "secondary primary malignancies" **Additional pharmacovigilance activities:** None
For MCL (mantle cell lymphoma) or FL (follicular lymphoma): TFR	**Routine risk minimisation measures:** Section 4.2 of SmPC advice on dose interruption Section 4.4 of SmPC warning Listed as ADRs in Section 4.8 of SmPC. **Additional risk minimisation measures:**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse reaction follow-up questionnaire for risk of "tumour flare reaction" **Additional pharmacovigilance activities:**

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Educational information for healthcare professionals	None
Cardiac failure	**Routine risk minimisation measures:** Listed as ADRs in Section 4. 8 of SmPC Listed in PL **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse reaction follow-up questionnaires for risk of "cardiac failure" **Additional pharmacovigilance activities:** None
Cardiac arrhythmias	**Routine risk minimisation measures:** Listed as ADRs in Section 4. 8 of SmPC Listed in PL **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse reaction follow-up questionnaires for risk of "cardiac arrythmias" **Additional pharmacovigilance activities:**
Ischaemic heart disease (including myocardial infarction)	**Routine risk minimisation measures:** Myocardial infarction is included in Sections 4.4 and 4.8 of the SmPC. **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse reaction follow-up questionnaires for risk of "ischaemic heart disease (including myocardial infarction)" **Additional pharmacovigilance activities:** None
Off-label use	**Routine risk minimisation measures:** Collection of off-label use data detailed in Section 4.4. of SmPC **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.3 is acceptable.

Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Product information

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 Emtricitabine/Tenofovir Krka d.d 200/245mg film coated tablets package information leaflet for visual presentation and Revlimid 2.5mg, 5mg, 7.5mg, 10mg, 15mg, 20mg, 25mg hard capsules package information leaflet for content.

3. Benefit-risk balance

This application concerns a generic version of lenalidomide hydrochloride monohydrate hard capsules. The reference product Revlimid is indicated for:

Multiple myeloma

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

Lenalidomide Krka 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.

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

No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The bioequivalence studies form the pivotal basis with a randomised, two-period, two-treatment

crossover design. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Lenalidomide Krka. met the protocol-defined criteria for bioequivalence when compared with the Revlimid. The point estimates and their 90% confidence intervals for the parameters AUC_{0-t} and C_{max} were all contained within the protocol-defined acceptance range of 80.00 to 125.00%. Bioequivalence of the two formulations was demonstrated.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Lenalidomide Krka is favourable in the following indications:

Multiple myeloma

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

Lenalidomide Krka 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.

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

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

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 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 Krka are provided with a physician information pack containing the following:
    - Educational health care professional's kit
    - Educational brochures for patients
    - Patient cards
    - 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 on the implementation of the patient card system in each Member State.

Key elements to be included

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
    - 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 Lenalidomide Krka for healthcare professionals and caregivers
- Obligations of the health care professional in relation to the prescribing of Lenalidomide Krka
    - 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 Krka
    - 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 Krka to be dispensed
    - Description of risk of tumour flare reaction
    - Description of risk of SPM
- Description of the PPP and categorisation of patients based on sex and childbearing potential
    - Algorithm for implementation of 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 Krka 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 contraception (even if man has had a vasectomy)
        - During Lenalidomide Krka treatment
        - For at least 7 days following final dose.
    - That if his partner becomes pregnant whilst he is taking Lenalidomide Krka or shortly after he has stopped taking Lenalidomide Krka he should inform his treating doctor immediately
- Requirements in the event of pregnancy

    - Instructions to stop Lenalidomide Krka 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 Krka to be dispensed
- That the patient should not give Lenalidomide Krka 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 Krka 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 sterilisation
    - After finishing treatment
- The need to stop Lenalidomide Krka 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 man has had vasectomy)

- During Lenalidomide Krka 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 Krka 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

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

The Member States should ensure that all conditions or restrictions with regard to the safe and effective use of the medicinal product described below are implemented:

1. The Member state shall agree the details of a controlled distribution system with the Marketing authorisation holder (MAH) according to national regulations and healthcare system and must implement such programme nationally to ensure that:

Prior to prescribing (and where appropriate, and in agreement with MAH, prior to dispensing) all healthcare professionals who intend to prescribe (and dispense) Lenalidomide Krka are provided with a physician information pack containing the following:

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

2. The Member State shall ensure that the MAH implements a prevention programme (PPP) within their territory. Details of the PPP including the set-up of national measures to assess the effectiveness of and compliance with 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.

3. The Member state should agree the final text of the healthcare professional's information pack contents with the MAH and ensure that the materials contain the key elements as described below.

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

Key elements to be included

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
    - 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 Lenalidomide Krka for healthcare professionals and caregivers
- Obligations of the health care professional in relation to the prescribing of Lenalidomide Krka
    - 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 Krka
    - 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 Krka to be dispensed
    - Description of risk of tumour flare reaction
    - Description of risk of SPM
- Description of the PPP and categorisation of patients based on sex and childbearing potential
    - Algorithm for implementation of 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 Krka 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 contraception (even if man has had a vasectomy)

        - During Lenalidomide Krka treatment
        - For at least 7 days following final dose.
    - That if his partner becomes pregnant whilst he is taking Lenalidomide Krka or shortly after he has stopped taking Lenalidomide Krka he should inform his treating doctor immediately
- Requirements in the event of pregnancy
    - Instructions to stop Lenalidomide Krka 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 Krka to be dispensed
- That the patient should not give Lenalidomide Krka 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 Krka 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 sterilisation
    - After finishing treatment
- The need to stop Lenalidomide Krka 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 man has had vasectomy)
    - During Lenalidomide Krka 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 Krka 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