26 July 2018
EMA/CHMP/563114/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lenalidomide Accord

International non-proprietary name: lenalidomide

Procedure No. EMEA/H/C/004857/0000

Note

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

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List of abbreviations

ABCB1	Human P-glycoprotein
ADR	Adverse drug reaction
AE	Adverse event
AML	Acute myeloid leukaemia
ANOVA	Analysis of Variance
ASCT	Autologous Stem Cell Transplantation
AST	Aspartate Aminotransferase
AUC	Area Under Curve
AUC0-∞	Area under the plasma concentration versus time curve from
AUC0-t	Area under the plasma concentration-time curve from drug
BCS	Biopharmaceutics Classification System
bFGF	Basic Fibroblast Growth Factor
BMSC	Bone Marrow Stromal Cells
CD34+	Cluster of differentiation 34+
CDK	Cyclin-Dependent Kinase
CI	Confidence Interval
Clast/Kel	where Clast is the last concentration above LLOQ
CLcr	Creatinine Clearance
Cmax	Maximum measured concentration of drug in plasma
CMV	Cytomegalovirus
DNA	Deoxyribonucleic Acid
ESRD	End-stage Renal Disease
GCP	Good Clinical Practice
gp	Glycoprotein
IFN	Interferon
IL	Interleukin
Kel	Elimination Rate Constant
KRD	Carfilzomib, Lenalidomide, Dexamethasone
Ln	Natural Logarithmic
LPS	Lipopolysaccharide
MAA	Marketing Authorization Application
MCL	Mantle-cell lymphoma
MDS	Myelodysplastic syndrome(s)
MM	Multiple myeloma
MPp	Melphalan, Prednisone, Placebo
MPR	Melphalan, Prednisone, Lenalidomide
MPT	Melphalan, Prednisone, Thalidomide
NDMM	Newly Diagnosed Multiple Myeloma
NDMM	Newly diagnosed multiple myeloma
NK	Natural Killer
NMSC	Non-melanoma skin cancer
NYHA	New York Heart Association
ORR	Overall Response Rate
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cells
PFS	Progression-free Survival
Rd	Lenalidomide Plus low-dose Dexamethasone
RD	Lenalidomide Plus Standard-dose Dexamethasone
RRMCL	Relapsed or refractory MCL
RRMM	Relapsed and/or refractory MM
SAS	Statistical Analysis System
SD	Standard Deviation
t1/2	Elimination Half Life
TFR	Tumour flare reaction
time zero	extrapolated to infinity [AUC0-∞ = AUC0-t +

Tmax	Time of the maximum measured plasma concentration
TNF-α	Tumor Necrosis Factor Alpha
TTP	Time To Progression
ULN	Upper Limit of Normal
VAD	Vincristine, Doxorubicin, Dexamethasone
VEGF	Vascular Endothelial Growth Factor
VRD	Bortezomib, Lenalidomide, Dexamethasone

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Accord Healthcare Limited submitted on 29 July 2017 an application for marketing authorisation to the European Medicines Agency (EMA) for Lenalidomide Accord, 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 22 June 2017.

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

Lenalidomide Accord as combination therapy (see section 4.2) is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant.

Lenalidomide Accord in combination with dexamethasone is indicated for the treatment of multiple myeloma in adult patients who have received at least one prior therapy.

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 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 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Revlimid; 5 mg, 10 mg, 15 mg, 25 mg; Capsule, hard
- Marketing authorisation holder: Celgene Europe Limited, United Kingdom
- Date of authorisation: (19-06-2007)
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/07/391/001-004, -008, -0010-0011

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

- Product name, strength, pharmaceutical form: Revlimid; 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 25 mg; Capsule, hard
- Marketing authorisation holder: Celgene Europe Limited, United Kingdom
- Date of authorisation: (19-06-2007)

- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/07/391/001-0011

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; 25 mg; Capsule, hard
- Marketing authorisation holder: Celgene Europe Limited, United Kingdom
- Date of authorisation: (19-06-2007)
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number(s): EU/1/07/391/004
- Bioavailability study number(s): 1605010

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.

Scientific advice

The applicant did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Ewa Balkowiec Iskra

The application was received by the EMA on	29 July 2017
The procedure started on	17 August 2017
The Rapporteur's first Assessment Report was circulated to all CHMP members on	3 November 2017
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	20 November 2017
The CHMP agreed on the consolidated List of Questions to be sent to	14 December 2017

the applicant during the meeting on	
The applicant submitted the responses to the CHMP consolidated List of Questions on	28 March 2018
The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	7 May 2018
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	17 May 2018
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	31 May 2018
The applicant submitted the responses to the CHMP List of Outstanding Issues on	26 June 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	20 July 2018
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 Accord on	26 July 2018

2. Scientific discussion

2.1. Introduction

This centralised application concerns a generic application according to article 10(1) of Directive 2001/83/EC for Lenalidomide Accord 2.5mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg & 25 mg hard capsules.

Lenalidomide has anti-inflammatory, immunomodulatory, anti-proliferative and antiangiogenic properties. It inhibits the secretion of pro-inflammatory cytokines including TNF-α, interleukin (IL)-1β, IL-6 and IL-12 from lipopolysaccharide (LPS)-stimulated peripheral blood mononuclear cells (PBMC) (Muller GW., et al., 1999 and Corral LG., et al., 1999). It also increases production of the anti-inflammatory cytokine IL-10 by LPS-stimulated PBMC and consequently inhibits the expression, but not the enzymatic activity, of cyclooxygenase-2 (Fujita J., et al., 2001). Lenalidomide induces T-cell proliferation and IL-2 and interferon (IFN)-γ production (Corral LG., et al., 1999 and Schafer PH et al., 2003) and it augments cytotoxic activity of natural killer cells Davies (FE., et al., 2001) (Armoiry X., et al., 2008).

The originator product is Revlimid; Lenalidomide was first approved in Europe on 14 June 2007 as Revlimid 5 mg, 10 mg, 15 mg, 25 mg (MAA No: EU/1/07/391/001-0011, Celgene Europe Limited, UK).

Multiple myeloma

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

Revlimid as combination therapy (see section 4.2) is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant.

Revlimid in combination with dexamethasone is indicated for the treatment of multiple myeloma in adult patients who have received at least one prior therapy.

Myelodysplastic syndromes

Revlimid as monotherapy is indicated for the treatment of adult patients with transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate.

Mantle cell lymphoma

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

One bioequivalence (BE) study has been performed using the originator. The test product (Lenalidomide Accord 25 mg hard capsule, Batch number: RLCH0616A) and the reference product (Revlimid 25 mg hard capsule, Batch number: A2106I-A) were compared in the fasting conditions (Study No. 1605010).

The generic Lenalinomide Accord claims only the originators indications in Multiple myeloma:

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

The originator's indications related to MS and MCL have not been applied for, as these indications are under "Orphan Market Exclusivity" until 17/06/2023 and 12/07/2026, respectively. Additionally, Celgene has a patent covering the MCL indication until 02/08/2027 (EP2046331).

Lenanidomide Accord will be presented as hard capsules in the same strengths as the originator's: 2.5mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg & 25 and with the same dose and posology in the above indications.

2.2. 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 as active substance.

Other ingredients are:

Capsule content: lactose, microcrystalline cellulose, croscarmellose sodium, colloidal anhydrous silica, magnesium stearate;

Capsule shell: gelatin (all), titanium dioxide (E171) (all), iron oxide black (E172) (2.5 mg), iron oxide red (E172) (7.5 mg, 15 mg), iron oxide yellow (E172) (10 mg, 15 mg), indigo carmine (E132) (7.5 mg, 10 mg).

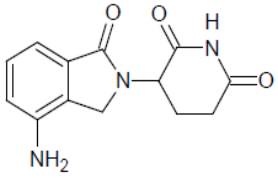
The product is available in OPA AL PVC/aluminium foil perforated unit dose blisters in a pack size of 7x1 or 21x1 capsules as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of lenalidomide is 3-(4-amino-1-oxo-2,3-dihydro-1*H*-isoindol-2-yl) piperidine-2,6-dione corresponding to the molecular formula $C_{13}H_{13}N_3O_3$. It has a relative molecular mass of 259.2 g/mol and the structure shown in Figure 1.

Figure 1: active substance structure



Lenalidomide active substance is an off-white to pale yellow solid powder, non-hydroscopic, soluble in organic solvent/water mixtures, and buffered aqueous solvents. Lenalidomide is generally more soluble in organic solvents but exhibits the greatest solubility in 0.1 N HCl buffer. The solubility of lenalidomide in water and at pH 1.21 is <1.5 mg/mL and 18 mg/mL, respectively.

The chemical structure of lenalidomide was elucidated and confirmed by a combination of proton nuclear magnetic resonance spectroscopy (1H NMR), carbon nuclear magnetic resonance spectroscopy (13C NMR), mass spectrometry (MS), infra-red spectroscopy and elemental analysis.

Lenalidomide has an asymmetric carbon atom and can therefore exist as the optically active forms S(-) and R(+). Lenalidomide is produced as a racemic mixture with a net optical rotation of zero. It has been demonstrated, by specific optical rotation results on 3 batches, that the active substance manufacturer consistently produces the racemate.

Lenalidomide exhibits polymorphism. Literature shows that lenalidomide exists in at least 8 different crystalline forms (Forms A-H) in addition to an amorphous form. The polymorphic form of lenalidomide active substance was measured by X-ray powder diffraction, and differential scanning calorimetry. It has been demonstrated that the active substance manufacturer consistently produces the same polymorphic form. The polymorphic form is controlled in the final active substance via identification testing by XRPD and DSC.

Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance has been provided in the restricted part of an ASMF and it was considered satisfactory. The ASMF holder is the single supplier of lenalidomide. A number of sites are involved in the manufacturing process.

Lenalidomide is synthesized in four main steps using well defined starting materials with acceptable specifications.

During the procedure, a major objection was raised in relation to the choice of starting materials. In response, the applicant provided further justification of the choice of one of the starting materials. The other initially proposed starting material was re-designated as an intermediate and the starting material was redefined further upstream. The details of the justification and updated synthetic route (reaction conditions, times, controls etc..) are in the restricted part of the ASMF. Based on this additional information this major objection was resolved.

The specifications and control methods for intermediate products, starting materials and reagents have been presented. Adequate in-process controls are applied during the synthesis. The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised. Presented specified process related organic impurities are well characterised by chemical name, structural formula, origin, specification and elucidation of structure (1H NMR, 13C NMR and MS). Potential degradation products of lenalidomide are described in detail.

During the procedure, the absence of a discussion on impurities with a genotoxic potential was raised as a major objection. In response a detailed discussion on impurities with a genotoxic potential risk was provided. Lenalidomide active substance itself is known to be teratogenic. The ASMF holder provided data on potential genotoxic impurities in the active substance and applies an acceptable control strategy for genotoxic impurities by setting appropriate limits, calculated with respect to the TTC, in in-process controls, intermediate specifications and active substance specifications. As a result of the redefinition of the starting material, additional impurity characterisation studies were performed and an updated impurity control strategy was provided. Based on the responses and additional information provided this major objection was resolved.

Information in relation to residual solvents and catalysts has been provided. Class-II solvents used in the last step of the synthesis are controlled in the active substance specification. No class-1 solvents are used in the synthesis.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program, changes implemented during development were described and justified.

The active substance packaging material has been described.s, It complieswith the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for appearance, identification (IR, HPLC, XRPD, DSC), solubility (Ph. Eur.), water content (Ph. Eur.), residue on ignition (Ph. Eur.), heavy metals (Ph. Eur.), related substances (HPLC), assay (HPLC), residual solvents (GC-HS, GC), microbial limit test (Ph. Eur.) and particle size distribution.

Impurities limits have been set below the qualification threshold according to ICH Q3A and in line with the TTC according to ICH M7.

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 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 one production scale batch of active substance stored for up to 12 months under long term conditions (25 ºC / 60% RH), and three production scale batches stored under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. These batches were produced by the proposed manufacturer using the commercial synthetic route and were stored in the intended commercial package.

Supportive stability data from three production scale batches of active substance from the proposed manufacturer using a slightly different synthetic route stored in the intended commercial package for up to 48 months under long term conditions (25 ºC / 60% RH) and up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were also provided. These batches are considered to be representative and therefore support the shelf-life, as the only difference when using different bases is an increase in yield without any impact on product quality.

The stability indicating parameters as outlined in the specification above were tested. The analytical methods used were the same as for release and were stability indicating. All tested parameters were within the specifications.

Results on stress conditions studies under acid, base, oxidation, thermal, photolytic and humidity conditions) were provided on one batch. Assay and degradation products were tested. Lenalidomide active substance is degraded under acid, base, oxidation forced degradation conditions.

The stress stability study of lenalidomide was carried out for determination of polymorphic form under stress stability study. The results of polymorphic form by XRPD confirmed that lenalidomide polymorphic form is stable under stress condition of humidity and temperature.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period and storage conditions in the proposed container.

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 and 25 mg of lenalidomide as active substance. The different hard capsule strengths are appropriately differentiated by their colour and size.

For 2.5 mg: Hard Gelatin Capsule shell of (Size “5”), cool grey cap and opaque white body with “LENALIDOMIDE” printed on cap in black and “2.5 mg” printed on body in green.

For 5 mg : Hard Gelatin Capsule shell of (Size “5”), opaque white cap and body with “LENALIDOMIDE” printed on cap in black and “5 mg” printed on body in green.

For 7.5 mg : Hard Gelatin Capsule shell of (Size "4"), opaque lavender cap and opaque white body with "LENALIDOMIDE" printed on cap in black and "7.5 mg" printed on body in green.

For 10 mg : Hard Gelatin Capsule shell of (Size "3"), leaf green cap and opaque white body with "LENALIDOMIDE" printed on cap in black and "10" mg" printed on body in green. printed on body in green.

For 20 mg : Hard Gelatin Capsule shell of (Size "1"), opaque green cap and opaque white body with "LENALIDOMIDE" printed on cap in black and "20 mg" printed on body in green **.**

For 25 mg : Hard Gelatin Capsule shell of (Size "0"), white opaque cap and body with "LENALIDOMIDE" printed on cap in black and "25 mg" printed on body in green.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The main objective of the formulation development was to develop a stable and robust formulation of "Lenalidomide 2.5mg, 5mg, 7.5mg, 10mg, 15mg, 20mg and 25mg hard capsules" which is essentially similar to reference product Revlimid® hard capsules marketed by Celgene Europe Limited, United Kingdom.

Quality by Design (QbD) principles were applied during the development of Lenalidomide Accord hard capsules. The formulation development strategy involved:

- Physicochemical characterisation of reference product
- Risk assessment of formulation variables
- Formulation development
- Formula optimisation
- Stability studies
- Update of risk assessment of formulation variables

The quality target product profile (QTPP) was defined based on the properties of the active substance, reference product characterization and intended patient population as immediate release hard capsules, for oral administration, which meet the compendial requirements for relevant quality attributes, with adequate stability in the chosen blister pack container. Pharmaceutical development was focused on CQAs and how these were impacted by changes on formulation or manufacturing process. The CQAs identified were assay, content uniformity, dissolution and related substances. Risk assessment was used throughout development to identify risks in formulation and process variables and to determine which studies were necessary to improve product and process understanding to develop a suitable control strategy. The QTPP is considered appropriate in view of the intended use of the product. The choice of the CQA that were studied during development is considered reasonable. Some of the process parameters initially anticipated to have significant effect on the release profile drug product were further studied and found to have insignificant effect on the drug release characteristics. Taking this under consideration not all CQAs are part of the finished product specification. This approach is justified based by the presented development data. The formulation composition was finalised based on development and optimisation studies.

A bioequivalence study was performed of Lenalidomide Accord 25 mg hard capsule versus the reference product, Revlimid 25 mg hard capsules. The bio-batch represents a registration (commercial) batch size and has been fully characterised. In support of the request for a biowaiver to cover the lower strengths in the product range, the Applicant presented comparative dissolution studies of Lenalidomide Accord hard capsules 2.5mg, 5mg, 7.5mg, 10mg, 15mg, 20mg with Lenalidomide Accord hard capsules 25mg. For all strengths, more than 85% of the labelled amount of lenalidomide was released in 0.01N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer, within 15 minutes. Therefore, the dissolution profiles are considered similar without further mathematical calculations. As supportive data, the applicant also presented comparative dissolution studies of Lenalidomide Accord hard capsules 2.5mg, 5mg, 7.5mg, 10mg, 15mg, 20mg, 25 mg with Revlimid hard capsules 2.5mg, 5mg, 7.5mg, 10mg, 15mg, 20mg and 25 mg, respectively.

According to the EMA product-specific bioequivalence guidance for lenalidomide hard gelatin capsules, lenalidomide is a compound with complete absorption. The development of the generic product Lenalidomide hard capsules concerns all strengths that are registered in the EU: 2.5mg, 5mg, 7.5mg, 10mg, 15mg, 20mg and 25mg. As presented in Table 1, the qualitative composition of the reference and the generic products are similar; only silica colloidal anhydrous is added to the Lenalidomide Accord. The justification for the inclusion of silica colloidal anhydrous is related to the manufacturing process.

Table 1 Comparison of list of excipients in test product and reference product

Excipient in test product	Excipient in reference product
Lactose	Lactose
Cellulose, microcrystalline	Cellulose, microcrystalline
Croscarmellose sodium	Croscarmellose sodium
Silica, colloidal anhydrous	--
Magnesium stearate	Magnesium stearate
Hard gelatin capsules	Hard gelatin capsules

A discussion on the potential impact of the differences in excipients quantitative contents on bioequivalence was provided. During the procedure a major objection was raised in relation to the difference in composition between the 2.5 mg and 5 mg strengths, and whether this impacts the acceptability of the biowaiver for the 2.5 mg strength. Based on the applicant's responses, it was concluded that, from the quality point of view there is little difference in composition between the 2.5 and 5 mg capsules, and considering the rapid dissolution of the active substance across the pH range, no differences that would merit a bioequivalence study are expected. To justify this approach, the Applicant provided literature data and results carried out *in vitro*. Lenalidomide is a BCS class-I drug, has high solubility and high permeability. Therefore, according to these results, the bioavailability of lenalidomide should not be affected by the amount of lactose used in the formulation. While the questions raised during the procedure asked the applicant to focus on the general biowaiver criteria, the applicant's responses focused on the BCS-biowaiver criteria. Nevertheless, based on the total information provided, the CHMP concluded that a further BE study is not required and the biowaiver for 2.5 mg strength can be accepted.

The impurity profile of Lenalidomide capsules manufactured by finished product manufacturer as per the final formula was compared with the impurity profile of reference product. The impurity profiles of the two products were found to be comparable. A risk assessment on elemental impurities in accordance with ICH

Q3D was also presented and considered acceptable. Justification for selection of the QC dissolution medium and apparatus has been provided. The discriminatory power of dissolution method was investigated and has been demonstrated.

The primary packaging is OPA AL PVC/Aluminium foil perforated unit dose blisters in a pack size of 7x1 or 21x1 capsules. 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 below main steps:

1. Sifting and blending
2. Pre-lubrication
3. Lubrication / blending
4. Filling of the capsules
5. Packaging.

The process is considered to be a standard manufacturing process. The in-process controls and intermediate specifications are adequate for this type of manufacturing process and pharmaceutical form. Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form. They include: description/appearance, identification (HPLC, UV), uniformity of dosage units (Ph. Eur.), average fill weight, water content (Ph. Eur.), disintegration time (Ph. Eur.), dissolution (Ph. Eur.), assay (HPLC), related substances (HPLC) and microbial enumeration test (Ph. Eur.).

The analytical methods used have been adequately described and 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 results are provided for three full scale batches of each strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from three production scale batches of each strength of finished product stored for up to 12 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for description, average fill weight, disintegration time, water content, dissolution, assay, related substances and microbial enumeration. The analytical procedures used are stability indicating. No significant changes have been observed.

Two batches of low and high strength (2.5mg & 25 mg) capsules were subjected to forced degradation studies under the following stress conditions: acid degradation, base degradation, peroxide degradation (oxidation), thermal degradation, heat and humidity degradation. The test methods were demonstrated to be stability indicating.

One batch (25 mg strength) was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The results showed the product is not significantly sensitive to photo degradation, so no special storage precaution is required for Lenalidomide Accord capsules.

Two batches of low and high strength (2.5mg & 25 mg) capsules were subjected to a temperature excursion study to evaluate the effect of transportation on the stability of the product in final its packaging (Alu-Alu blister pack). Samples were stored under -20ºC for 2 days followed by exposure to 60ºC and 75% RH for 2 days. This thermal cycle was repeated 3 times and samples were withdrawn at the end of each cycle. The samples were found to be stable.

Stability study results for bulk capsules packed in double lined polybag, placed in stainless steel container, and stored up to 60 days, before being primary packaging were also provided. There were no significant changes in tested parameters up to 60 days. Therefore, a 30 day hold time for the bulk capsules is accepted.

Based on available stability data, the proposed shelf-life of 2 years with no special storage conditions as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

Appropriate statements confirming TSE/BSE compliance were provided from the suppliers of the excipients derived from animal origin, i.e. lactose and gelatin.

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 Lenalidomide Accord 25 mg hard capsule and the reference product, Revlimid 25 mg hard capsules, and biowaivers have been accepted for the other strengths; 2.5mg, 5mg, 7.5mg, 10mg, 15mg, and 20mg.

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.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. 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 report refers 33 publications up to year 2017. 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 was submitted. This was justified by the Applicant as the introduction of Lenalidomide 2.5, 5, 7.5, 10, 15, 20 and 25 mg hard capsules manufactured by Accord 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 and not increased.

2.3.3. Discussion on non-clinical aspects

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

The CHMP considers that the non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate. The Applicant presented a non-clinical discussion, including a description of expected impurities and their acceptability thresholds, which is acceptable. The non-clinical data is reflected in the appropriate sections of the SmPC. In line with the requirements for generic products, no new non-clinical data was submitted and none is expected.

There are no objections to approval of Lenalidomide Accord 2.5, 5, 7.5, 10, 15, 20 and 25 mg hard capsules from a non-clinical point of view.

2.3.4. Conclusion on the non-clinical aspects

In line with the requirements for generic products, no new non-clinical data was submitted, which is acceptable.

The non-clinical information for Lenalidomide as in the PI of Revlimid applies also to Lenalidomide Accord and reflected in the RMP and risk minimization measures as necessary.

2.4. Clinical aspects

2.4.1. Introduction

This marketing authorisation application under the centralised procedure concerns a generic application according to article 10(1) of Directive 2001/83/EC for Lenalidomide Accord 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).

One bioequivalence (BE) study has been performed using the originator. The test product (Lenalidomide Accord 25 mg hard capsule) and the reference product (Revlimid 25 mg hard capsule) were compared in the fasting conditions(Study No. 1605010). The clinical overview dated 26.04.2017; the report refers to 39 publications up to year 2017. It seems adequate in term of bibliographic data on clinical pharmacology, efficacy and safety of lenalidomide. This is accepted by CHMP.

For the clinical assessment the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98) as well as the Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/09) are of particular importance.

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

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

Lenalidomide 20mg, 15mg, 10mg, 7.5mg, 5mg capsules (test product) were compared with Lenalidomide 25 mg capsules (test bio-batch). An In-vivo bioequivalence study of Lenalidomide 25 mg Hard Capsules with Revlimid® 25 mg Hard Capsules was conducted under fasting conditions and test product was found bioequivalent to reference product.

Based on the acceptable bio-equivalence study for Lenalidomide 25 mg capsules, a request for waiver of bio-study on remaining strength i.e. 2.5/5/7.5/10/15/20 mg is being placed based on the following general requirements contained in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1).

According to the EMA guideline on the investigation of bioequivalence; following general requirements must be met where a waiver for additional strength(s) is claimed:

a) All the strengths i.e. 2.5/5/7.5/10/15/20 mg and 25 mg of proposed pharmaceutical product are manufactured by the same manufacturing process,

b) The qualitative composition of the Lenalidomide capsules 2.5/5/7.5/10/15/20 mg is same as that of Lenalidomide capsules 25 mg.

c) The composition of the all strengths i.e. 5/7.5/10/15/20 mg and 25 mg are quantitatively proportional i.e. the ratio between the amount of each excipient to the amount of active substance(s) is same for all the strengths.

d) In-vitro dissolution data on all the strengths confirms the adequacy of waiving additional in-vivo bioequivalence testing

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. Elimination is primarily renal. Following a single oral administration of [14C]-lenalidomide (25 mg) to healthy subjects, approximately 90% and 4% of the radioactive dose is eliminated within ten days in urine and feces, respectively. Approximately 82% of the radioactive dose is excreted as lenalidomide in the urine within 24 hours. The same has been reported in the innovator literature that lenalidomide has been classified as BCS Class I molecule. Lenalidomide capsules were developed as a scale down dose proportional formulation for 25, 20, 15, 10, 7.5 & 5 mg capsules.

Comparative in-vitro dissolution study:

The dissolution profile of Lenalidomide hard capsules 20/15/10/7.5/5 mg (Exhibit batches) was compared with Lenalidomide 25 mg hard capsules (test bio-batch) manufactured by Reliance life sciences Pvt. Ltd.

Table 2: Dissolution conditions:

Medium	Apparatus	Volume	Temperature	RPM
0.01N HCl (QC medium)	Basket	900 mL	37 ± 0.5°C	100
0.1 N HCl				
pH 4.5 Acetate buffer				
pH 6.8 Phosphate buffer				

Comparative dissolution studies of Lenalidomide hard capsules 20 mg, 15 mg, 10 mg, 7.5 mg, 5 mg with Revlimid hard capsules 20 mg, 15 mg, 10 mg, 7.5 mg, 5 mg and Lenalidomide hard capsules 25 mg were carried out. More than 85% of Lenalidomide were released within 15 minutes. Therefore, dissolution profiles may be accepted as similar without any mathematical calculation for similarity.

In Vitro Dissolution Testing of Batches Used in Bioequivalence Study

The Applicant's batch of Lenalidomide 25 mg hard capsules and batch of Revlimid 25 mg hard capsules were used in the bioequivalence study. Dissolution study of Lenalidomide hard capsules 25 mg with Revlimid hard capsules 25 mg were carried out. More than 85% of Lenalidomide were released within 15 minutes.

Moreover, additional comparative dissolution studies of Lenalidomide hard capsules 20 mg, 15 mg, 10 mg, 7.5 mg, 5 mg with Revlimid hard capsules 20 mg, 15 mg, 10 mg, 7.5 mg, 5 mg were carried out . As in the case of 25 mg hard capsules, more than 85% of Lenalidomide or Revlimid were released within 15 minutes. Therefore, dissolution profiles may be accepted as similar.

Based on the dissolution results obtained, it can be concluded that test and reference product for all the strengths are releasing more than 85% of drug within 15 minutes. Release profiles of test product strengths are similar to each other and with the corresponding strengths of reference product.

The Applicant provided in-vitro dissolution profile comparison between test bio-batch strength (25 mg) and biowaiver strengths (20 mg, 15 mg, 10 mg, 7.5 mg and 5mg) in accordance with EMA guidance (Guideline on

the Investigation of Bioequivalence - CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **, section 4.2.2). Dissolution data obtained confirms the adequacy of waiving additional in-vivo bioequivalence testing.

The Applicant provided in-vitro dissolution profile comparison between test bio-batch strength (25 mg) and biowaiver strengths (20 mg, 15 mg, 10 mg, 7.5 mg and 5mg). In all cases, the dissolution test revealed that more than 85% of the drug was dissolved within 15 min (range 91-100%). Therefore, according to the relevant guideline the dissolution profiles of the drugs were accepted as similar without further mathematical evaluation.

Bio-waiver for 2.5 mg strength

Lenalidomide capsules were developed as a scale-down dose proportional formulation for 25, 20, 15, 10, 7.5 and 5 mg capsules.

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. The same has been reported in the innovator literature that Lenalidomide has been classified as BCS Class I molecule.

Solubility Profile

To demonstrate the highly soluble nature of the molecule, the highest dose of the drug substance i.e. 25 mg of Lenalidomide was taken and dissolved in 250 mL of various physiological buffer in the range of pH 1.2, 4.5 & 6.8 along with water, were studied using a stability indicating method, each pH was studied in replicate and for 24 hours. The pH before and after were recorded as per the required guideline.

Sample preparation procedure

Accurately weighed and transferred about 25 mg of Lenalidomide API into a 500 mL flask. Added 250 mL of respective media. Kept on shaker at 37°C for 24 hours at 50 rpm.

Table 3: Solubility profile

S. No.	Medium	pH of Media		BCS solubility 37°C (mg/250 ml)	Solubility at 37°C (mg/ml)			
		before drug substance addition	after drug substance addition		Sample 1	Sample 2	Sample 3	Mean
1	Water	5.76	5.75	25	0.098	0.098	0.099	0.10
2	0.01 N HCl	1.39	1.36	25	0.102	0.099	0.100	0.10
3	0.1 N HCl	1.19	1.18	25	0.099	0.099	0.098	0.10
4	pH 4.5 Acetate buffer	4.60	4.58	25	0.100	0.098	0.098	0.10
5	pH 6.8 Phosphate buffer	6.84	6.84	25	0.099	0.099	0.099	0.10
6	pKa (pH = 2.3)	2.23	2.23	25	0.098	0.098	0.098	0.098

As per the definition in the guidelines, the solubility results reveal that Lenalidomide belongs to a class of highly soluble drugs with maximum dose i.e. 25 mg is dissolving in less than 250 ml of media across the pH profile.

Therapeutic index

BCS-based biowaiver is restricted to highly soluble drug substances with known human absorption and considered not to have a narrow therapeutic index. Lenalidomide does not have a narrow therapeutic index and highly soluble BCS class I drug substance.

The dissolution results indicate that both the test and reference formulation are releasing more than 85 % of the drug product within 15 minutes hence classifying the formulation as very rapidly releasing formulation. The test product 25 mg capsules have shown bio-equivalence to reference product 25 mg capsules and has similar qualitative composition to test product 2.5 mg capsules.

Excipients

The test product does not contain any excipient which is known to alter the bioavailability of the active moiety and the excipients incorporated are qualitatively similar to the reference product except Silica, colloidal anhydrous which is added as a processing aid in a minute concentration. Other excipients are used in the usual effective concentrations ranges well below IID levels.

Table 4: Excipients

Inactive Ingredients	Amount per unit (mg)/capsule	IID levels (Orals) Maximum potency (mg)
	2.5mg	
Lactose	35.96	735.20
Cellulose, microcrystalline	28.00	1553.00
Croscarmellose Sodium	2.80	180.00
Silica, colloidal anhydrous	0.60	170.00
Magnesium stearate	0.14	4384.00

The Applicant presented comparative dissolution studies of Lenalidomide hard capsules 20 mg, 15 mg, 10 mg, 7.5 mg, 5 mg with Revlimid hard capsules 20 mg, 15 mg, 10 mg, 7.5 mg, 5 mg and Lenalidomide hard capsules 25 mg, that were carried out . More than 85% of Lenalidomide were released within 15 minutes. The sampling time points are sufficient. Bearing in mind that more than 85% of the labelled amount of the drug was released within 15 minutes from each tested formulations (all the batches), the dissolution profiles could be considered as similar without further mathematical calculations. Bearing in mind the fact that all requirements contained in the guideline CPMP/EWP/QWP/1401/98 Rev. 1/ Corr** for 25, 20, 15, 10, 7.5 and 5 mg capsules (the same manufacturing process, proportional formulation for all strength, similar qualitative and quantitative compositions) are fulfilled, these strength may be considered for biowaiver.

Clinical studies

To support the application, the applicant has submitted one bioequivalence study, 1605010.

Table 5: Tabular overview of clinical studies

To support the application, the Applicant has submitted one bioequivalence study.

Type of study	Study identifier	Objective of the study	Study design and type of control	Test products, dosage regimen; route of administration	Number of subjects	Healthy subjects or diagnosis of patients	Duration of treatment	Study status
BE	Study no. 1605010	Primary 1. To assess the bioequivalence of single dose test formulation of Lenalidomide 25 mg Hard Capsules of Reliance Life Sciences Pvt. Ltd., India with reference Revlimid® (containing 25 mg of Lenalidomide) of Celgene Europe Limited, in normal, healthy, adult, male subjects under fasting conditions. Secondary 1. To monitor the adverse events and ensure the safety of subjects 2. To collect other pharmacokinetic data of the Testand Reference formulations.	A randomized, open-label, single dose, two-treatment, two-sequence, two-period, crossover bioequivalence study under fasting conditions.	Test: Lenalidomide 25 mg hard capsule of Reliance Life Sciences Pvt. Ltd., India (proposed for registration) Reference: Revlimid® (containing 25 mg of Lenalidomide) hard capsules of Celgene Europe Limited single-dose (25 mg) oral administrations	Enrolled 54, Completed 52	Healthy adult human subjects	A single oral dose of either the test or reference product was administered in one period.	Completed

2.4.2. Pharmacokinetics

Study no. 1605010

Methods

Study design

The Applicant has submitted a comparative bioequivalence study. The Principal Investigator (PI) provided the IEC with all appropriate study documents.

This was a randomized, open-label, single-dose, two-treatment, two-sequence, two-period, crossover bioequivalence study of test Lenalidomide 25 mg hard capsule with reference Revlimid® (containing 25 mg of Lenalidomide) of Celgene Europe Limited, in healthy, adult, male subjects under fasting conditions. The

objectives of the study were: a) To assess the bioequivalence of single dose test formulation of Lenalidomide 25 mg Hard Capsules with reference Revlimid® (containing 25 mg of Lenalidomide) of Celgene Europe Limited, in normal, healthy, adult, male subjects under fasting conditions.; b) to monitor the adverse events and ensure the safety and to collect other pharmacokinetic data of the Test and Reference formulations.

The administration of test and reference products to each subject of the study was determined according to the randomization schedule. The personnel involved in the dispensing of investigational products would be accountable for ensuring compliance to randomization schedule. All subjects who were randomized into the study are included. The randomization schedule was provided in submitted documentation.

The study was conducted between 18/10/2016 and 02/11/2016 and bioanalysis was performed between 05.11.2016 – 19.11.2016.

Within this clinical trial, there were 2 different treatments. The treatments were defined as follows:

- oral fasted administration of one hard capsule of test product
- oral fasted administration of one hard capsule of reference product

The administration of Test and reference products to each subject of the study was determined according to the randomization schedule. The personnel involved in the dispensing of investigational products would be accountable for ensuring compliance to randomization schedule. The analyst concerned did not have access to randomization schedule during the course of analysis.

During all treatment periods, blood samples of approximately 6 ml volume were taken. Blood samples were taken at the following time points.

The blood samples were collected in pre-labelled (mentioning study number, subject number, period and sampling time point) sodium heparin vaccutainer.

All the collected blood samples were taken for centrifugation in a refrigerated centrifuge, in order to separate plasma. The resulting plasma from each blood sample were divided into two aliquots and stored in suitably pre labelled polypropylene tubes, until the assay was performed.

The quantification of lenalidomide in plasma was performed using a validated Liquid Chromatography Coupled with Tandem Mass Spectrometry (LC-MS/MS).

The study was performed under fasting conditions. According to the reference product SmPC recommendation (Revlimid, SmpC), the drug can be taken with or without food. According to the Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **), in such circumstances a bioequivalence study should be conducted under fasting conditions. The subjects were administered a single oral dose of 25 mg of Lenalidomide of either the test or reference product at a particular stage of the study.

The sampling periods are acceptable with sample time points around Tmax for lenalidomide and with an adequate wash-out period (at least 6 treatment-free days) at greater than five times the t1/2 (2.5 hours for lenalidomide). The sampling frequency allowed for adequate estimation of Cmax. The sampling schedule covered the plasma concentration time curve that was long enough to provide a reliable estimate of the extent of exposure.

The sample shipment condition, method of temperature control during transportation and timespan between blood sampling and freezing of samples are documented in sample transfer records.

Test and reference products

The reference product Revlimid (25 mg) is approved in the European Union (MA Holder: Celgene Europe Limited) and was purchased from the UK market. Prior to start of the clinical trial the reference product was checked with respect to the relevant parameters of pharmaceutical quality, especially in-vitro dissolution and content. Batches used for the clinical trial were of appropriate quality and were manufactured according to GMP standards.

Certificates of analysis for both the test and reference products have been provided. Assay values of 96.8% and 100.3% for the test and reference are reported respectively. The assayed content of the batch used as test product did not differ more than 5% from that of the batch used as reference product which is in accordance with the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 01 Corr**).

Population(s) studied

The current study was done with 54 subjects to demonstrate bioequivalence between Test formulation and the corresponding Reference product. Based on literature data, the maximum intra-subject variability observed for primary pharmacokinetic parameter (AUC and Cmax,) was found to be 22% for Lenalidomide. The sample size computation was determined considering the following assumptions:

- T/R ratio ~ 90-111 %
- Intra-Subject C.V (%) ~22 %
- Significance Level = 5%
- Power ≥ 80%
- Bioequivalence Limits = 80.00-125.00%

Based on above data calculated sample size n=54 (considering 10% dropouts and/or withdrawals), will be sufficient to establish bioequivalence with adequate power for the pivotal study.

Fifty four healthy, adult, human subjects participated under fasting conditions and 52 subjects completed both the periods of the study. Subject no. 032 did not report for period II check-in. One subject did not participate in period II as he was found positive for alcohol breath test during period II check in. For comparative pharmacokinetic and statistical analysis, 52 subjects were considered. All 54 subjects were considered for safety evaluation.

Inclusion criteria

1. Healthy adult male subjects, aged between 18 to 45 years.
2. Subjects with Body Mass Index (BMI) 18.5 to 24.9 kg/m2
3. Subjects able and willing to comply with the protocol requirements.
4. Subjects willing to voluntarily provide written informed consent.
5. Subjects willing to undergo pre- and post-study physical examinations and laboratory investigations.
6. Subjects who are non-smokers based on history.
7. Subjects willing to adhere to the protocol and the study requirements:

- Should not consume xanthine containing products, such as coffee, tea, chocolate or soft drinks at least 48 hours prior to dosing (i.e. in-house monitoring and the remaining based on history) until the last sample collection.
- Should not consume alcohol at least 48 hours prior to dosing (i.e. during in house monitoring and the remaining based on history) until the last sample collection.
- Should not consume grapefruit or its products at least 7 days prior to each dosing (i.e. during in-house monitoring and the remaining based on history) and until the last sample collection.

8. Subjects having no clinically significant medical history and no clinically significant abnormalities in general physical examination, laboratory assessments, 12-lead ECG, chest X-Ray or vital signs.
9. Men must agree to use medically acceptable methods of contraception during the study and for 30 days after the last study drug administration.

Exclusion criteria

1. Subjects incapable of understanding the informed consent process.
2. Subjects with inadequate venous access in their left or right arm to allow the collection of all samples via venous cannula in the study.
3. Subjects with abnormalities in resting heart rate, blood pressure either hypotensive episode or hypertension, oral temperature on the screening day.
4. Subjects with active history of psychiatric disorders, which are likely to limit the validity of consent to participate in the study, or limit the ability to comply with the protocol requirements.
5. Subjects with any evidence of organ dysfunction or any clinically significant deviation from normal in their physical or clinical evaluation including ECG and X-ray results.
6. Subjects who have taken over the counter or prescribed medications.
7. Subjects with a known history of drug hypersensitivity to Lenalidomide or any excipients of the formulation.
8. Subjects with a history of alcohol abuse and/or drug abuse or who are found urinary screen test positive for drugs of abuse (Amphetamines, Morphine, Benzodiazepines, Marijuana, Cocaine and Barbiturates) or are found with current alcohol abuse based on alcohol breath test.
9. Subjects diagnosed to be HIV 1 and 2 or Hepatitis B (HBsAg) or Hepatitis C (HCV) virus positive.
10. Subjects with clinically significant abnormal haematological values [haemoglobin (Hb), total white blood cells count (WBC), total red blood cells count (RBC), differential WBC count, platelet count and hematocrit].
11. Subjects with clinically significant abnormal laboratory values for serum creatinine, blood urea nitrogen (BUN), serum aspartate aminotransferase (AST), serum alanine aminotransferase (ALT), serum alkaline phosphatase (ALP), serum bilirubin, serum glucose (fasting), and serum cholesterol.
12. Subjects with lymphocytes below the lower limit of normal range at screening.
13. Subjects with clinically significant abnormal urine analysis, defined as the presence of RBC (>5/HPF), pus cells (>5/HPF), epithelial cells (>5/HPF), glucose (positive), ketones (positive), bilirubin

(positive) and protein (positive) (unless the clinical investigator considers the deviation to be irrelevant for the purpose of the study).

14. Subjects with a clinically significant past history or current medical condition of: pulmonary disorders (COPD and asthma), cardiovascular disorders (especially heart blocks, myocardial infarction, congestive heart failure and uncontrolled hypertension), neurological disorders (especially epileptic seizures), GIT disorders (gastrointestinal bleeding, gastric/peptic ulcer), renal and/or hepatic disorders.

Protocol deviations

There was no protocol deviation reported in the study. However, subject no. 032 did not report for period II check-in. Subject no. 035 did not participate in period II as he was found positive for alcohol breath test during period II check in.

In the presented study sample size calculation was properly conducted.

The inclusion and exclusion criteria are acceptable and drawn up according to the protocol. All subjects are observed and treated according to the same rules. The data from all treated subjects was treated in the same way.

The study population is appropriate and the main inclusion and exclusion criteria are in line with the requirements of the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 01). According to the protocol calculations, 54 subjects were considered to be enough to power the study with 52 subjects completing the study.

The Applicant presented a list of pre-specified reasons that may be used to remove subjects form therapy assessment. Some of them may be deemed clearly arbitrary (eg. Investigator's discretion and sponsor's decision). The Applicant is asked to explain what precisely lies behind these statements?

Analytical methods

Lenalidomide in plasma samples was analysed by use of a validated Liquid Chromatography Coupled with Tandem Mass Spectrometry; Lower Limit of Quantitation (LLOQ) for lenalidomide was 2.015 ng/ml. In the presented clinical trial a bioanalytical method based on LC with MS/MS detection after liquid-liquid extraction from plasma was utilized.

Validation of the test method

The method has been validated. The following parameters were addressed: selectivity for lenalidomide and internal standard (investigation of interference caused by blank plasma, by haemolysed blank plasma and hyperlipidaemic blank plasma), carryover, matrix effect (influence of haemolysed plasma and hyperlipidaemic plasma), linearity, lower limit of quantification (with acceptable precision and accuracy), precision, accuracy, recovery rate and stability. Each parameter has been assessed and the limits are justified. This is deemed acceptable.

The analytical method used to determine the concentration of lenalidomide in human plasma seems to be adequately described; the validations were performed according to the requirements of the EMA "Guideline on bioanalytical method validation" (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**)". Acceptance criteria are in a plausible range.

The validation activity was initiated by using structural analogue “Indapamide” which is also compatible with lenalidomide as an internal standard. The method was fully validated using Indapamide as internal standard. Upon the availability of isotopic labelled compound, the method was partially validated using isotopic labelled internal standard.

The analytical methods used are acceptable. The calibration curves are appropriate and the stability testing justifies the conditions the samples were exposed to during collection and testing. The Applicant has also provided relevant supportive data together with certificates of analysis for the analyte standard and internal standards used in the analytical method validation. Moreover, the partial validation report due to changing of internal standard is also presented.

Bioanalytical report

The bioanalytical report dated 02 Nov 2016 was submitted. The quantification of lenalidomide in plasma was performed using a validated Liquid Chromatography-Mass spectrometry/Mass spectrometry (LC-MS/MS) method. The lower limit of quantitation of the method was 2.0 ng/ml, the upper limit of quantitation was 751.0 ng/ml for lenalidomide. Lenalidomide 13C5 was used as internal standard.

The total number of analysed study samples was 2226. The total number of repeated samples was 53.

The study samples were identified by the study number, subject number and sampling time point. Details for dropout subjects and missing samples are available in sample transfer record. Study samples will be stored under frozen conditions at -70±15ºC and records shall be maintained in respective logbooks.

In this study the total number of study samples measured was 2226. In total 2.38 % of the samples were repeated.

The Applicant presented bioaanalysis results of the BEQ study. The quantification of lenalidomide in plasma was performed using a validated Liquid Chromatography-Mass spectrometry/Mass spectrometry (LC-MS/MS) method. The lower limit of quantitation of the method was 2.0 ng/ml, the upper limit of quantitation was 751.0 ng/ml for lenalidomide. Lenalidomide 13C5 was used as internal standard. The bioanalysis was performed between 05.11.2016 to 19.11.2016. The total number of analysed study samples was 2226.

During the bioanalysis fifty three study samples had to be reanalysed. Fifty one samples needed to be reanalysed due to concentration above upper limit of quantification. This contributes to only 2.3% of the total study samples. Additionally, dilution integrity experiment was already completed during the method validation for handling such cases. During repeat analysis, diluted quality control (QC) samples were also processed to check the acceptance of the dilution applied during the analysis. As diluted QC samples were well within the acceptance limits, it is proposed that the effect of dilution will not have any impact on study results.

During conduct of the study, documentation of haemolysed samples was done in Sample Receipt and Accountability Form for each time point. A total of 62 samples were haemolysed. There was no defined procedure for identification of lipemic samples in Clinical Pharmacology Unit (CPU) at the time of conduct of the study. In reference to this regulatory query, the identification of lipemic samples was done retrospectively. The samples stored in deep freezer were retrieved by Clinical Trial Supplies Management Representative and received by Bioanalytical Lab (BL). The identification of lipemic samples was done by CPU representative, manually checking the physical appearance of each sample, in presence of representative from BL and Quality Assurance group on 23 Nov 2017. A total of 63 samples were found to be lipemic.

There is a high chance of false positive or false negative interpretation during identification of lipemic samples due to following reasons.

• Identification was done manually by checking physical appearance of samples.

• These samples had already undergone multiple freeze thaw cycles (not more than five) which could lead to hazy appearance of some samples. Similarly some lipemic may have cleared due to prolonged storage.

Further, we would like to inform agency that two lots each of haemolysed and lipemic samples are processed and analysed in selectivity and matrix effect experiment during method validation. The response of lipemic and haemolysed samples were in precision with the other normal lots in both the above experiments, hence there is no impact of these samples on the quantitation of analyte.

Storage period of study samples

The bioanalysis was performed between 05.11.2016 to 19.11.2016. Long term stability was determined for 55 days at -20^{0}C and -70^{0}C. This time span was sufficient as time between withdrawal of first PK sample and last analytical measurement did not exceed 31 days.

Incurred Sample Reanalysis

In this study the scheduled total number of subject samples was 2226. Incurred sample reanalysis was performed on 168 samples (7.55%). As a criterion of acceptance two thirds of the repeat samples should agree within ± 20 %. In total, 97.62 % of the repeat samples agreed within ± 20 %. Therefore the acceptance criteria were fulfilled and incurred sample reanalysis was in accordance with the European guideline.

The analytical portion of the bioequivalence study (Study No. RLS/0715/019) was conducted according to a validated method (ACC Project-No.: VR-16-004-LLM) and EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2** guideline on Shimadzu LC20 and AB Sciex (API-3000 and API-3200), using Lenalidomide 13C5 as internal standards (IS). Some issues need to be elucidated.

Pharmacokinetic Variables

The following pharmacokinetic parameters were determined from the time and concentration data of Lenalidomide, using non-compartmental model of Phoenix WinNonLin® version 6.4 Pharsight application or higher version:

Cmax Maximum measurable plasma concentration.

AUC0-t Area under the plasma concentration versus time curve from drug administration to last observed concentration at time t.

AUC0-∞ Area under the plasma concentration versus time curve from time zero extrapolated to infinity.

Tmax Time of maximum measured plasma concentration. If the maximum value occurs at more than one time point, Tmax is defined as the first time point.

t1/2 Elimination or terminal half-life.

Kel Elimination rate constant.

For all the above computations, actual time points of the sample collection were used. No value of Kel, AUC0-∞ and/or t1/2 was reported for cases that do not exhibit a terminal log-linear phase in the concentration

versus time profile; however, if Cmax and Tmax could still be reliably estimated then these PK parameters were included in the statistical analysis.

Pharmacokinetics parameters evaluated in presented study were appropriate to determine bioequivalence. The primary pharmacokinetic variables were Cmax, and AUC0-t. Also software used in analyse was well known and sufficient.

Statistical methods

The statistical analysis was performed on pharmacokinetic parameters of Lenalidomide using SAS®, statistical software Version 9.3; SAS Institute Inc., USA. The number of subjects (N), Geometric Mean, Arithmetic Mean, Median, Standard deviation, Minimum, Median, Maximum, Coefficient of variation were calculated. Summary statistics were calculated for plasma concentrations of Lenalidomide, at each time point as well as for the pharmacokinetic parameters for the Test and Reference product separately.

Ln-transformed pharmacokinetic parameters Cmax, AUC0-t and AUC0-∞ and untransformed pharmacokinetic parameters Cmax, AUC0-t, AUC0-∞, Tmax, Kel, AUC0-t/ AUC0-∞ and t1/2 were evaluated statistically using the PROC GLM procedure of SAS®. For Average bioequivalence approach, the statistical model ANOVA contained main effects of sequence, period, products & subject within sequence. The F test were performed to determine the statistical significance of the effects involved in the model at 5% level of significance (p=0.05). Two one-sided 90% confidence intervals for the ratio of means between Test and Reference products were calculated for Ln-transformed data of pharmacokinetic parameters Cmax and AUC0-t and were found to be within 80% to 125% to establish bioequivalence. For untransformed Tmax non parametric test (Wilcoxon sign rank test) was applied.

The protocol contained section about missing data management and outliers as follows: the data from subjects with missing concentration values (missed blood samples, lost samples, samples unable to be quantified) may be used if pharmacokinetic parameters can be estimated using remaining data points, otherwise data from these subjects will be excluded from the final analysis. Any missing samples or non-reportable concentration values will be reported as "Missing" or "Non-Reportable Values" (NRV). No concentration estimates will be calculated for missing values. BLQ values will be treated as zero for Pharmacokinetic Analysis.

The raw data generated during the course of the study including the clinical, analytical and statistical operations along with the final report underwent quality assurance audit for conformance to the study protocol and all the governing SOPs, by auditors from the Quality Assurance Unit.

For retrospective calculation of study power, SAS system 9.3 was used. The equivalence test mean ratio statistical test was used for computation of power. From the study, the observed mean ratio and observed CV% has been used to compute power for sample size of 52 subjects who were considered for PK analysis with BE limits 80.00-125.00% and level of significance (α=0.05%). As stated above the variables used for computation of power for all primary PK parameters are presented below which shows that computed power for all PK parameters are >80%. The post study power calculation for Cmax and AUC showed that study was adequately powered to test the equivalence between test and reference arm.

Descriptive statistics and data handling procedures (missing data management and outliers detecting methods) were properly designed and clearly presented. As the visualizations of study results were legible. Statistical methodology established in SAP was mostly consistent with guidelines and properly conducted.

Statistical evaluation of pharmacokinetic data was performed with analysis of variance methodology, with fixed effects. Significant formulation effect was observed for lnAUC0-t. However the applicant has provided detailed explanation related to this result.

Results

Pharmacokinetic Parameters

Pharmacokinetic measurements assessed were based on the parameters derived from the plasma concentration versus time data of individual subjects. For Test and Reference products, mean Cmax was 671.83 and 651.61 ng/mL, AUC0-t was 2308.83 and 2257.62 (ng X hr/mL) and AUC0-∞ was 2333.56 and 2281.29 (ng X hr/mL) respectively. The median tmax observed for Test and Reference products was 0.83 hrs.

Table 6: Descriptive Statistics of Pharmacokinetic Parameters of lenalidomide under fasting conditions for Test Product

Variable	N	Mean	SD	Min	Median	Max	CV (%)
C_{max}	52	671.83	129.63	415.82	659.58	996.83	19.29
AUC_{0-t}	52	2308.83	376.05	1609.28	2319.64	3343.66	16.29
$AUC_{0-\infty}$	52	2333.56	379.56	1635.04	2333.64	3407.69	16.27
T_{max}	52	0.95	0.48	0.5	0.83	2.67	50.32
$t_{1/2}$	52	3.67	0.62	2.49	3.73	5.16	17.01
K_{el}	52	0.19	0.04	0.13	0.19	0.28	18.19
$AUC_{extraob}$	52	1.07	0.51	0.43	0.93	2.85	47.75

Table 7: Descriptive Statistics of Pharmacokinetic Parameters of lenalidomide under fasting conditions for Reference Product

Variable	N	Mean	SD	Min	Median	Max	CV (%)
C_{max}	52	651.61	155.29	377.49	629.83	1043.56	23.83
AUC_{0-t}	52	2257.62	356.78	1632.61	2212.01	3111.68	15.8
$AUC_{0-\infty}$	52	2281.29	361.83	1662.49	2228.13	3163.89	15.86
T_{max}	52	0.96	0.47	0.5	0.83	2	48.95
$t_{1/2}$	52	3.63	0.56	2.61	3.76	4.75	15.39
K_{el}	52	0.2	0.03	0.15	0.18	0.27	16.29
$AUC_{extraob}$	52	1.04	0.53	0.38	0.84	2.61	50.89

The geometric means T/R ratios for lnCmax, lnAUC0-t and lnAUC0-∞ were 104.13%, 102.20% and 102.24% respectively which were within the range of 80 to 125%. For T Vs R, the 90% confidence intervals ranges for lnCmax from, 97.89 - 110.77 for lnAUC0-t 100.51 - 103.92 and for lnAUC0-∞ 100.59 - 103.91 which were within the limit of 80.00-125.00%.

Analysis of Tmax

The Tmax is comparable between Test and Reference product and no significant difference was observed between two arms as assessed by Wilcoxon scores (Rank sums) test for Tmax (P=0.93).

Table 8: Summary Statistics of Ln-transformed Pharmacokinetic Parameters by for lenalidomide for T Vs. R

Variable	Reference (R)	Test (T)	100*(T/R) Ratio	CI (%)	Intra CV	Power
C_{max} (ng/mL)	634.32	660.52	104.13	97.89 - 110.77	18.97	99.99
AUC_{0-t}(ng x hr/mL)	2232.44	2281.47	102.20	100.51 - 103.92	5.08	100.00
$AUC_{0-\infty}$ (ng x hr/mL)	2255.79	2306.23	102.24	100.59 - 103.91	4.94	100.00

ANOVA: Assessment of Sequence, Period and Formulation Effects

Table 9: Analysis of Variance (ANOVA) of the lnCmax and lnAUC0-t

Parameter	Source	DF	Type III SS	Mean Square	F Value	Pr > F
$lnAUC_{0-t}$	Formulation	1	0.01225185	0.01225185	4.76	0.0338
	Period	1	0.00094264	0.00094264	0.37	0.5477
	Subject(Sequence)	50	2.41951350	0.04839027	18.81	<.0001
	Sequence	1	0.06995868	0.06995868	1.45	0.2349
lnC_{max}	Formulation	1	0.04254485	0.04254485	1.20	0.2778
	Period	1	0.00186080	0.00186080	0.05	0.8194
	Subject(Sequence)	50	2.91443468	0.05828869	1.65	0.0399
	Sequence	1	0.04336986	0.04336986	0.74	0.3925

Figure 2: Mean plasma concentration vs. time curves of lenalidomide after oral single dose administration of test and reference products.

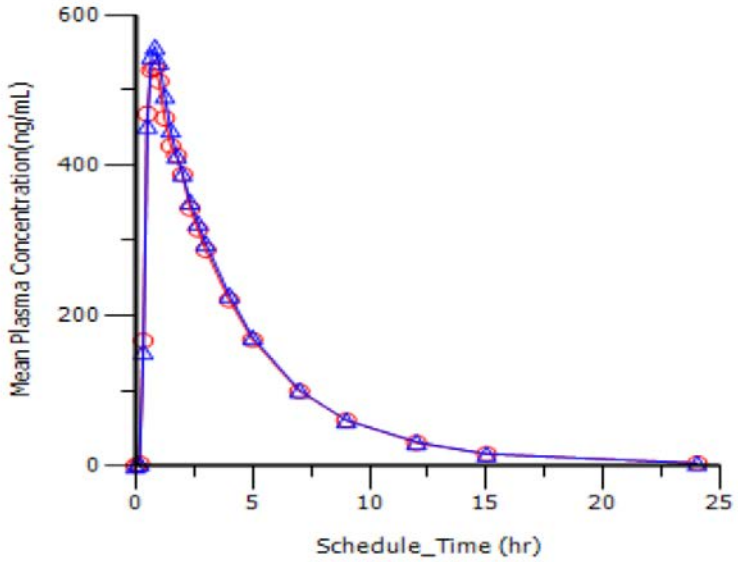
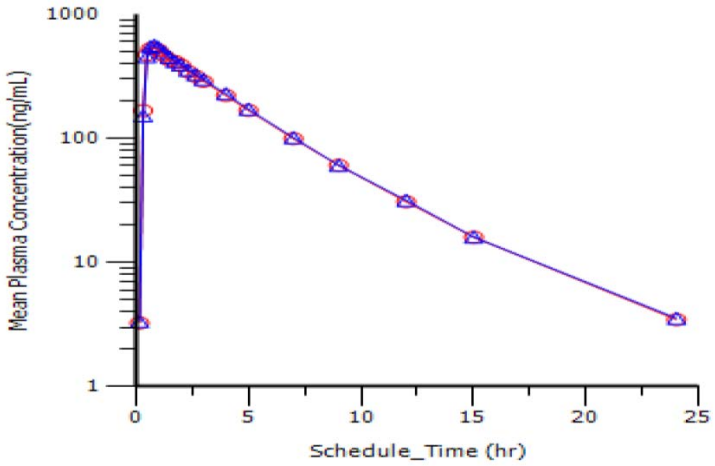


Figure 3: Mean plasma concentration vs. time curves of lenalidomide after oral single dose administration of test and reference products, semi-logarithmic plot.



The plasma concentration profile for both the formulation showed comparable pharmacokinetics as represented in mean linear and mean semi log linear graphs shown above.

The ratios of the mean of the ln-transformed data (T/R ratio) for lnCmax and lnAUC0-t were 104.13 and 102.20 respectively for Lenalidomide. For mean ratio T/R, the 90% confidence intervals for lnCmax ranges from 97.89 - 110.77 and for lnAUC0-t ranges from 100.51 - 103.92 which were within the bioequivalence range of 80.00% - 125.00% for Lenalidomide. It can be concluded Test Lenalidomide 25 mg hard capsule is bioequivalent with reference Revlimid® (containing 25 mg of Lenalidomide) of Celgene Europe Limited, in normal, healthy, adult, male subjects under fasting conditions.

Safety data

Extent of exposure

Fifty-two subjects received 1 tablet of Test and Reference products. As subject no. 032 did not report for period II check-in and subject no. 035 did not participate in period II (as he was found positive for alcohol breath test during period II check in), two subjects received 1 tablet of Test product. Therefore, drug exposure was 1 x 25 mg of lenalidomide in each period. Hence, total dose of 52 subject was 2 x 25 mg resulting in 50 mg lenalidomide. Extent of exposure in the case of subjects no. 032 and 035 was 1 x 25 mg lenalidomide in total.

Adverse events (AEs)

In this study, 2 adverse events were reported. There were 2 (3.70%) subjects reported with adverse events in Reference arm. Both the AEs reported in the reference arm were mild in severity. One AE was possibly related and another was probably reported. There was no adverse event reported in Test arm. The one AE was from general disorders and administration site conditions system organ class (SOC) and second AE was from investigation SOC class.

Analysis of Adverse Events

Subject no. 029 following administration of reference product in period I had fever on 20/10/16 at 14:24 hrs. It was mild in severity and probably related to study drug. It resolved on 20/10/16 at 14:24 hrs. Subject no. 019 following administration of reference product in period II had high fasting glucose level i.e. 133.0 mg/dl on 27/10/16 at 09:09 hrs during post study safety evaluation. The first repeat was performed on 29/10/16 and fasting blood glucose level decreased to 129.1 mg/dl. It was clinically significant. The second repeat was performed on 02/11/16 and fasting blood glucose level increased to 130.8 mg/dl. It was clinically significant. The third repeat was performed on 10/11/16 and random blood glucose level decreased to 89.7 mg/dl. It was within normal limit. The AE was mild in severity and possibly related to study drug. It resolved on 10/11/16 at 15:50 hrs.

The overall incidence of AEs was small. They occurred in the Reference group only. The AE was mild in severity and possibly related to study drug.

Clinical laboratory evaluation

All the values of pre-study laboratory measurements were within the normal laboratory range and any values that were slightly outside the normal laboratory range were judged to be clinically not significant.

Evaluation of each laboratory parameter

Laboratory parameters including hematology, biochemistry profile and urine analysis of the study subjects, undertaken at pre-study screening and post-study safety assessment revealed that the values of most parameters were within the normal range for most of the subjects. There were some cases that were slightly outside the normal laboratory range and according to the clinician were not considered to be clinically significant, either due to the value being not significantly elevated or reduced, being an isolated finding with no other abnormal laboratory findings or not being associated with any clinical findings.

Laboratory values over time

Screening laboratory examinations were performed for all randomised subjects. Following the exclusion criteria in the study protocol for certain laboratory parameters (CRP, ASAT, ALAT, bilirubin and creatinine) thresholds were defined.

In the screening laboratory examinations some subjects presented abnormal haematological values (haemoglobin (Hb), total white blood cells count (WBC), total red blood cells count (RBC), differential WBC count, platelet count and hematocrit).

The eligibility of subjects is assessed based on overall health status of the volunteers considering medical history, physical examination findings and laboratory reports. Work instruction titled “Acceptable Laboratory Test Range” (CP/WI/26) is referred to judge health status of subjects during conduct of the study. This document provides normal laboratory value ranges as well as guidance for assessing the clinical significance of laboratory values outside the normal range. Please refer to Appendix 5 for Acceptable Laboratory Test Range.

The lab reports received on the check in day before deciding eligibility of the volunteers were also checked. No subjects with clinically significant abnormality were included in the study. If any abnormalities were present; they were deemed not clinically significant by the investigator.

Vital signs, physical findings and other observations related to safety

No clinically relevant changes in the ECG parameters, vital signs and physical parameters related to safety were observed between screening and end of study examination.

Safety conclusions

Subjects who received at least a single dose of the study drug lenalidomide capsules (either test or reference) in the study were included in the safety analyses. In this study, all subjects were included in the safety analysis. No clinically significant change was noted with respect to blood pressure, body temperature and other vital parameters from baseline to end of the study.

In this study, 2 adverse events were reported. There were 2 (3.70%) subjects reported with adverse events in Reference arm. Both the AEs reported in the reference arm were mild in severity. One AE was possibly related and another was probably reported. There was no adverse event reported in Test arm. All adverse events reported in the study were resolved. No serious adverse event was observed in the study. The adverse events observed in this study were in line with the known safety profile of the product and were mild in severity. No major safety concerns were noted during this study with Test or Reference formulation. Based on safety analysis, it can be concluded that, both Test and Reference formulations are well tolerated during study.

Both products were found to be safe and well tolerated. There were no serious adverse events (AEs) reported in this study. The adverse events were not life threatening nor did they required the subjects to be hospitalized. After study drug intake, 2 subjects showed 2 AEs - 2 after reference treatment. This two AEs were classified as having possible or probable relationship to the investigational product. All AEs reported after study drug intake resolved completely. No subject dropped out due to AEs.

Conclusions

Based on the presented bioequivalence study 1605010 Lenalidomide Accord 25 mg hard capsule is

considered bioequivalent with Revlimid.

2.4.3. Pharmacodynamics

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

2.4.4. Post marketing experience

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

2.4.5. Discussion on clinical aspects

The bioequivalence study 1605010 was designed as a randomized, open-label, single-dose, two-treatment, two sequence, two-period, crossover bioequivalence study of test Lenalidomide 25 mg hard capsule with reference Revlimid® (containing 25 mg of Lenalidomide) of Celgene Europe Limited, in healthy, adult, human subjects under fasting conditions.

Sample size calculation was properly conducted based on the observed coefficient of variation (CV) as the study should have 54 evaluable subjects (with 10% dropout rate) to show the bioequivalence with a power greater than 80% at 5% level of significance; 54 healthy, adult, human subjects participated under fasting conditions and 52 subjects completed both the periods of the study. Subject no. 032 did not report for period II check-in. Subject no. 035 did not participate in period II as he was found positive for alcohol breath test during period II check in. For comparative pharmacokinetic and statistical analysis, 52 subjects were considered. All 54 subjects were considered for safety evaluation. The study population is appropriate and the main inclusion and exclusion criteria are in line with the requirements of the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 01). According to the protocol calculations, 54 subjects were considered to be enough to power the study with 52 subjects completing the study.

Pharmacokinetics parameters evaluated in presented study were appropriate to determine bioequivalence. The primary pharmacokinetic variables were Cmax, and AUC0-t. Also software used in analyse was well known and sufficient. Methodological assumptions, descriptive statistics and data handling procedures (missing data management and outliers detecting methods) were properly designed and clearly presented. Statistical methodology established in SAP was mostly consistent with guidelines and properly conducted. Statistical evaluation of pharmacokinetic data was performed with analysis of variance methodology, with fixed effects.

Safety evaluation by physical examination, vital signs, monitoring adverse events as clinical signs and symptoms during the study, and laboratory investigations performed at the end of the study revealed comparable safety profile. The adverse events observed in this study were in line with the known safety profile of the product. No new significant safety concerns were noted during this study with Test or Reference formulation. The adverse events observed in this study were in line with the known safety profile of the product and were mild in severity. No SAE was observed in the study. Upon conclusion of clinical portion, the results from the subjects who completed post study procedures including laboratory tests confirmed the absence of significant changes in the subject's state of health.

The observed concentration data for Lenalidomide was analysed. To assess the bioequivalence of the test product, the 90% confidence intervals were calculated for the geometric least square mean ratios (T vs R) of

the primary endpoints Cmax, and AUC0-t of Descriptive statistics of pharmacokinetic parameters for test and reference formulations shows mean Cmax was 671.83 and 651.61 ng/mL, AUC0-t was 2308.83 and 2257.62 (ng X hr/mL) and AUC0-∞ was 2333.56 and 2281.29 (ng X hr/mL) respectively. The median Tmax observed for both Test and Reference formulations was comparable (0.83 hrs for both Test and Reference product). The Tmax is comparable between Test and Reference product and no significant difference was observed between two arms as assessed by Wilcoxon scores (Rank sums) test for Tmax (P=0.93). The half-life of both Test and Reference formulations was comparable. (Mean T1/2 for T Vs R – 03.67 Vs 03.63 hrs).

Bioequivalence assessment showed that the ratios of the geometric least square mean of ln-transformed data (T/R ratio) for lnCmax, and lnAUC0-t were 104.13% [90% CI (97.89 - 110.77)], 102.20% [90% CI (100.51 - 103.92)] respectively which were within acceptable bioequivalence range. Analysis of Variance (ANOVA) of the lnCmax and lnAUC0-t obtained from the Test and Reference formulations shows no sequence and period effect with respect all ln transformed PK parameter.

The analytical method for the determination of lenalidomide in human plasma seems to be described adequately; the validations were performed according to the requirements of the EMA “Guideline on bioanalytical method validation” (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**)”. Acceptance criteria are in a plausible range. The analytical methods used are acceptable and appropriate.

The post study power calculation for primary pharmacokinetic parameters showed that study was adequately powered to test the equivalence between test and reference arm. In this study, 2 adverse events were reported. There were 2 (3.70%) subjects reported with adverse events in Reference arm. Both the AEs reported in the reference arm were mild in severity. One AE was possibly related and another was probably reported. There was no adverse event reported in Test arm. All adverse events reported in the study were resolved. No serious adverse event was observed; the adverse events in this study were in line with the known safety profile of the product and were mild in severity. No major safety concerns were noted during this study with Test or Reference formulation.

It can be concluded Test Lenalidomide 25 mg hard capsule is bioequivalent to reference Revlimid (containing 25 mg of Lenalidomide) of Celgene Europe Limited. All relevant information from the PI of Revlimid is reflected in the PI of Lenalidomide Accord.

2.4.6. Conclusions on clinical aspects

The presented study was designed and conducted according to recommendations of the EMA Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **). Based on the results obtained in the bioequivalence study (Study No.: 1605010, Protocol No.: RLS/0715/019), the Lenalidomide 25 mg hard capsule (Test) and Revlimid® (containing 25 mg of Lenalidomide) (Reference), is considered bioequivalent. Moreover, bearing in mind that all requirements contained in the guideline CPMP/EWP/QWP/1401/98 Rev. 1/ Corr** for 25, 20, 15, 10, 7.5, 5 and 2.5 mg capsules are fulfilled the results of the bioequivalence study could be extrapolate on these strengths.

The clinical aspects in Revlimid PI are reflected in the PI of Lenalidomide Accord.

2.5. Risk management plan

Safety concerns

Important identified risks	• Teratogenicity • Serious infection due to neutropenia • Second primary malignancies (SPM)
Important potential risks	• Cardiac failure • Cardiac arrhythmias • Ischaemic heart disease (including myocardial infarction) • Off-label use
Missing information	• None

Pharmacovigilance plan

Study; Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones** (required by regulators)	**Due dates**
Short title: Pregnancy prevention programme for Lenalidomide Accord (Category 3 study) Status: Planned	Monitoring of implementation and the effectiveness of PPP	Teratogenicity	Routine PSURs in-line with DLP of 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

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Important Identified Risks		
Teratogenicity	<u>Routine risk minimisation measures:</u> Section 4.3, 4.4, 4.6, 4.8 and 5.3 of Lenalidomide SmPC and corresponding section of PIL has information on this safety concern.	<u>Routine pharmacovigilance activity:</u> Routine pharmacovigilance activities including collection and reporting of adverse reactions and signal detection as stated in pharmacovigilance

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Other routine risk minimisation measures include the prescription only status of the product. Additional risk minimisation measures: Pregnancy Prevention Programme (PPP), HCP Brochure; Treatment algorithm, pregnancy reporting form, patient card, patient brochure and checklists	system master file. Specific follow-up questionnaires have been proposed for Teratogenicity. Additional pharmacovigilance activity: Pregnancy prevention programme for Lenalidomide Accord shall be implemented as Category 3 study.
Serious infection due to neutropenia	Routine risk minimisation measures: Section 4.2, 4.4 4.8 and 5.3 of Lenalidomide SmPC and corresponding section of PIL has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Additional risk minimisation measures: HCP Brochure	Routine pharmacovigilance activity: Routine pharmacovigilance activities including collection and reporting of adverse reactions and signal detection as stated in pharmacovigilance system master file. Specific follow-up questionnaires have been proposed for neutroprenia and infection Additional pharmacovigilance activity: None
Second primary malignancies (SPM)	Routine risk minimisation measures: Section 4.2, 4.4 and 4.8 of Lenalidomide SmPC and corresponding section of PIL has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Additional risk minimisation measures: HCP Brochure	Routine pharmacovigilance activity: Routine pharmacovigilance activities including collection and reporting of adverse reactions and signal detection as stated in pharmacovigilance system master file. Specific follow-up questionnaires have been proposed Other second primary malignancies (SPM). Additional pharmacovigilance activity: None
Important Potential Risks		
Cardiac failure	Routine risk minimisation measures: Section 4.8 of Lenalidomide SmPC and corresponding section of PIL has information on this	Routine pharmacovigilance activity: Routine pharmacovigilance activities including collection and reporting of adverse

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	safety concern. Other routine risk minimisation measures include the prescription only status of the product. Additional risk minimisation measures: None	reactions and signal detection as stated in pharmacovigilance system master file. Additional pharmacovigilance activity: None
Cardiac arrhythmias	Routine risk minimisation measures: Section 4.8 of Lenalidomide SmPC and corresponding section of PIL has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Additional risk minimisation measures: None	Routine pharmacovigilance activity: Routine pharmacovigilance activities including collection and reporting of adverse reactions and signal detection as stated in pharmacovigilance system master file. Additional pharmacovigilance activity: None
Ischaemic heart disease] (including myocardial infarction)	Routine risk minimisation measures : Section 4.4 and 4.8 of Lenalidomide SmPC and corresponding section of PIL has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Additional risk minimisation measures: None	Routine pharmacovigilance activity: Routine pharmacovigilance activities including collection and reporting of adverse reactions and signal detection as stated in pharmacovigilance system master file. Additional pharmacovigilance activity: None
Off-label use	Routine risk minimisation measures : Section 4.4 of Lenalidomide SmPC has information on this safety concern. Other routine risk minimisation measures include the prescription only status of the product. Additional risk minimisation measures: None	Routine pharmacovigilance activity: Routine pharmacovigilance activities including collection and reporting of adverse reactions and signal detection as stated in pharmacovigilance system master file. Additional pharmacovigilance activity: None

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.2 is acceptable.

2.6. 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.

2.7. Product information

2.7.1. 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 Revlimid. The bridging report submitted by the applicant has been found acceptable.

2.7.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Lenalidomide Accord is included in the additional monitoring list as it has conditions or restrictions with regard to the safe and effective use of the medicinal product.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-risk balance

This application concerns a generic version of Lenalidomide hard capsule. The reference product Revlimid is indicated for the maintenance treatment of adult patients with newly diagnosed multiple myeloma who have undergone autologous stem cell transplantation; as combination therapy for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant; in combination with dexamethasone for the treatment of multiple myeloma in adult patients who have received at least one prior therapy; as monotherapy for the treatment of adult patients with transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate; as monotherapy is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma.

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 study forms the pivotal basis. 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 Accord met the protocol-defined criteria for bioequivalence when compared with Revlimid. The point estimates and their 90% confidence intervals for the parameters AUC_{0-t},, $AUC_{0-\infty}$, and C_{max} were all contained within the protocol-defined acceptance range of [range, e.g. 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. The information included in the PI of Revlimid is reflected appropriately in the PI of Lenalidomide Accord. The risk minimisation plan and risk minimisation measures agreed for Revlimid apply also to Lenalidomide Accord.

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 Accord is favourable in the following indication:

Multiple myeloma

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

Lenalidomide Accord as combination therapy (see section 4.2) is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant.

Lenalidomide Accord in combination with dexamethasone is indicated for the treatment of multiple myeloma in adult patients who have received at least one prior therapy.

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

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

Key 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
- The need to avoid foetal exposure due to teratogenicity of lenalidomide in animals and the expected teratogenic effect of lenalidomide in humans

Obligations of the health care professional in relation to the prescribing of Lenalidomide Accord

- 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 Accord
- Need to provide patients with appropriate patient educational brochure and patient card

<u>Safety advice relevant to all patients</u>

- Description and management of neutropenia and thrombocytopenia including incidence rates from clinical trials
- Description and management of cutaneous reactions
- Description and management of hypersensitivity and angioedema
- Description and management of thromboembolic risk including incidence rates from clinical trials and post-marketing experience
- Use in patients with hepatic and/or renal impairment
- Disposal of unwanted medicine
- Local country specific arrangements for a prescription for Lenalidomide Accord to be dispensed
- Explanation of the risk of neuropathy with long term use
- 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 Accord 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 contraceptions (even if man has had a vasectomy)
    - During Lenalidomide Accord treatment
    - For one week following final dose
- That if his partner becomes pregnant whilst he is taking Lenalidomide Accord or shortly after he has stopped taking Lenalidomide Accord he should inform his treating doctor immediately

Requirements in the event of pregnancy

- Instructions to stop Lenalidomide Accord immediately upon suspicion of pregnancy
- 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

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 and their partners

☐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

- That Lenalidomide Accord may cause neutropenia and thrombocytopenia and the need for regular blood tests
- That Lenalidomide Accord may cause venous and arterial thromboembolism
- 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 Accord to be dispensed
- That the patient should not give Lenalidomide Accord to any other person
- That the patient should not donate blood
- 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, every 4 weeks except in case of confirmed tubal sterilisation
    - After finishing treatment
- The need to stop Lenalidomide Accord immediately upon suspicion of pregnancy
- The need to contact their doctor immediately upon suspicion of pregnancy

Brochure for male patients

- The need to avoid foetal exposure
- The need to use condoms if sexual partner is pregnant or a WCBP not using effective contraceptions (even if man has had vasectomy)
    - During Lenalidomide Accord treatment
    - For one week following final dose
- That if his partner becomes pregnant he should inform his treating doctor immediately

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 regards 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 Accord 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
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    - Before commencing treatment
    - During treatment based on method of contraception
    - After finishing treatment
- Need to stop Lenalidomide Accord 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 contraceptions (even if man has had a vasectomy)
    - During Lenalidomide Accord treatment
    - For one week following final dose
- That if his partner becomes pregnant whilst he is taking Lenalidomide Accord or shortly after he has stopped taking Lenalidomide Accord he should inform his treating doctor immediately

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Brochure for male patients

- The need to avoid foetal exposure
- The need to use condoms if sexual partner is pregnant or a WCBP not using effective contraceptions (even if man has had vasectomy)
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