15 October 2020
EMA/CHMP/583241/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lenalidomide Mylan

International non-proprietary name: lenalidomide

Procedure No. EMEA/H/C/005306/0000

Note

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

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Administrative information

Name of the medicinal product:	Lenalidomide Mylan
Applicant:	Mylan Ireland Limited Unit 35/36 Grange Parade Baldoyle Industrial Estate Dublin 13 IRELAND
Active substance:	Lenalidomide
International non-proprietary name/Common name:	lenalidomide
Pharmaco-therapeutic group (ATC Code):	immunosuppressants, other immunosuppressants (L04AX04)
Therapeutic indication(s):	Multiple myeloma Lenalidomide Mylan as monotherapy is indicated for the maintenance treatment of adult patients with newly diagnosed multiple myeloma who have undergone autologous stem cell transplantation. Lenalidomide Mylan as combination therapy with dexamethasone, or bortezomib and dexamethasone, or melphalan and prednisone (see section 4.2) is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant. Lenalidomide Mylan in combination with dexamethasone is indicated for the treatment of multiple myeloma in adult patients who have received at least one prior therapy. Follicular lymphoma Lenalidomide Mylan in combination with

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

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List of abbreviations

AAS	Atomic Absorption Spectrometry
AE	Adverse event
ALT	Serum alanine transaminase
ANOVA	Analysis of variance
ASMF	Active Substance Master File = Drug Master File
AST	Serum aspartate transaminase
AUC	Area under the curve
AUC0-∞	Area under the plasma concentration versus time curve to infinity
AUC0-t	Area under the plasma concentration versus time curve to the last measurable concentration (t)
BLQ	Below limit of quantitation
BMI	Body Mass Index
BUN	Blood urea nitrogen
CI	Confidence Interval
Cmax	Maximum observed plasma concentration
CMA	Critical Material Attribute
CPP	Critical process parameter
CQA	Critical Quality Attribute
CRF	Case report form
CTD	Common technical document
CV	Coefficient of Variation
CYP	Cytochrome P450
DSC	Differential Scanning Calorimetry
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
GCP	Good Clinical Practice
t1/2, HALFLIFE	Apparent terminal elimination half-life
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
HS-GC	Headspace Gas chromatography
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-MS	Inductively coupled plasma mass spectrometry
IEC	Institutional Ethics Committee
IR	Infrared
IRB	Institutional Review Board
ISCV	Intrasubject Coefficient of Variation
KEL	Elimination Rate Constant
l :	Litre
Ln :	Natural Logarithmic
LC/MS/MS	Liquid chromatography coupled to tandem mass spectrometry detection
LDPE	Low Density Polyethylene
LQC	Last quantifiable concentration
LSM	Least-squares means
MAA :	Marketing Authorisation Application
PK/DM	Pharmacokinetics/Drug Metabolism
MM	Multiple Myeloma
MDS	Myelodysplastic Syndrome
MCL	Mantle Cell lymphoma
MS	Mass Spectrometry
NMR	Nuclear Magnetic Resonance
QA	Quality Assurance
QC	Quality Control
QTPP	Quality target product profile
REB	Research Ethics Board
SAE	Serious Adverse Event
SD :	Standard Deviation

TEAE	Treatment emergent adverse event
TGA	Thermo-Gravimetric Analysis
Tmax	Time of maximum observed plasma concentration
XRPD	X-Ray Powder Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Mylan Ireland Limited submitted on 13 September 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Lenalidomide Mylan, 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 28 February 2019.

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

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

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

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

Follicular lymphoma

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

The legal basis for this application refers to:

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

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Revlimid instead of non-clinical and clinical 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 10 years in the EEA:

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

Marketing authorisation numbers:

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

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

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

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

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

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

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

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

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

  Marketing authorisation numbers:

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

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

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

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

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

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

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

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

- Product name, strength, pharmaceutical form: Revlimid 10 mg & 25 mg hard capsules
- Marketing authorisation holder: Celgene Europe BV
- Date of authorisation: 14-06-2007
  - Marketing authorisation granted by: Union

  Marketing authorisation numbers: 10mg: EU/1/07/391/002; 25mg: EU/1/07/391/004
- Bioavailability study number(s): Study LENA-18026 and Study LENA-18009

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 from the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP were:

Rapporteur: Eleftheria Nikolaidi Co-Rapporteur: N/A

The application was received by the EMA on	13 September 2019
The procedure started on	3 October 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	18 December 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	30 December 2019
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	30 January 2020
The applicant submitted the responses to the CHMP consolidated List of Questions on	24 April 2020
The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	2 June 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 June 2020
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	25 June 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	18 August 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	2 September 2020
The CHMP agreed on the 2nd list of outstanding issues in writing to be sent to the applicant on	17 September 2020
The applicant submitted the responses to the CHMP 2nd List of Outstanding Issues on	22 September 2020

The Rapporteurs circulated the Joint Assessment Report on the responses to the 2nd List of Outstanding Issues to all CHMP members on	30 September 2020
The Rapporteurs circulated the updated Joint Assessment Report on the responses to the 2nd List of Outstanding Issues to all CHMP members on	8 October 2020
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Lenalidomide Mylan on	15 October 2020

2. Scientific discussion

2.1. Introduction

Multiple Myeloma (MM) accounts for 1% of all cancers and 10% approximately of all haematological malignancies in Caucasians and 20% in African Americans (Dispenzieri A and Kyle RA, 2005; Moreau P et al., 2017). The incidence in Europe is 4.5-6.0/100 000/year with a median age at diagnosis of 72 years; the mortality is 4.1/100 000/year (Moreau P et al., 2017). The incidence of MM is about 1.5 times higher in males than in females. The prevalence of MM varies from country to country in the European Union (EU). Overall, the estimated prevalence of MM in the EU in 2018 ranges from 1.79 to 3.61 in 10,000 persons (EPAR-Assessment report, Revlimid, 2019).

Multiple myeloma is characterised by the uncontrolled proliferation of monoclonal plasma cells in the bone marrow, leading to production of non-functional intact immunoglobulins or immunoglobulin chains. Most patients with MM present with symptoms related to the infiltration of plasma cells into the bone or other organs or to kidney damage from excess light chains. The treatment of multiple myeloma is complex because of rapid advances in stem cell transplantation, medications, and better supportive care, which have led to improved survival over the past 30 years (Kumar SK et al, 2014). The main options for treatment include non-chemotherapy drugs that target the cancer cells, standard chemotherapy drugs, corticosteroids, and stem cell (bone marrow) transplant.

Follicular lymphoma (FL) is a systemic neoplasm of the lymphoid tissue displaying germinal centre (GC) B cell differentiation. FL represents approximately 5% of all haematological neoplasms and 20–25% of all new non-Hodgkin lymphoma diagnoses in western countries (Carbone et al., 2019).

Follicular lymphoma is characterised by diffuse lymphadenopathy, bone marrow involvement, and splenomegaly. Cytopenias are relatively common. In the absence of transformation to diffuse large B cell lymphoma constitutional symptoms of fever, night sweats, and weight loss are uncommon. The diagnosis is based on histology from a biopsy of a lymph node or other affected tissue. Immunohistochemical staining is positive in virtually all cases for cell surface CD19, CD20, CD10 and monoclonal immunoglobulin, as well as cytoplasmic expression of bcl-2 protein. The overwhelming majority of cases have the characteristic t(14;18) translocation involving the IgH/bcl-2 genes (Freedman et al, 2019). The choice of treatment for FL is highly dependent on patient and disease characteristics. In case of limited disease, treatment options include radiotherapy, rituximab monotherapy or combination regimens, and surveillance. For advanced disease, the treatment is often determined by tumour burden, with surveillance or rituximab considered for low tumour burden and chemoimmunotherapy for high tumour burden disease (Matasar et al., 2019).

This centralised application for marketing authorisation concerns a generic application according to Article 10(1) of Directive 2001/83/EC, as amended for Lenalidomide Mylan 2.5, 5, 7.5, 10, 15, 20 and 25 mg hard capsules. The originator product is Revlimid 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg

& 25 mg hard capsules (Celgene Europe Limited), which is currently approved in Europe.

The proposed medicinal product has for each strength the same qualitative and quantitative composition in active substance and the same pharmaceutical form compared to the reference product.

To support the application, the applicant submitted two bioequivalence studies between Mylan's lenalidomide capsules in strength of 10 mg and 25 mg and reference product, Revlimid Capsules 10 mg and 25 mg of Celgene Europe Limited, in order to assess bioequivalence between the products. A biowaiver of strength has been requested for the remaining strengths: 2.5mg, 5 mg, 7.5 mg, 15 mg, and 20 mg.

The proposed indication for the test product is as follows:

Multiple myeloma

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

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

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

During review of the procedure, the applicant applied for an additional indication of the reference product as it follows:

Follicular lymphoma

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

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, 25 mg of lenalidomide.

Other ingredients in the capsule contents (all strengths) are: pregelatinised starch, microcrystalline cellulose, croscarmellose sodium, colloidal anhydrous silica and sodium stearyl fumarate.

Other ingredients in capsule shells (all strengths) are: gelatin, titanium dioxide (E171).

Other ingredients in capsule shells are: yellow iron oxide (E172) (2.5 mg, 7.5 mg, 10 mg, 20 mg) black iron oxide (E172) (7.5 mg & 10 mg), Indigo carmine [E132] (2.5 mg, 10 mg, 20 mg).

Other ingredients in printing ink (all strengths) are: shellac, propylene glycol.

Other ingredients in printing ink (2.5 mg, 5 mg, 7.5 mg, 10 mg, 25 mg) are: black iron oxide (E172), potassium hydroxide.

Other ingredients in printing ink (15 mg, 20 mg) are: red iron oxide (E172), simethicone.

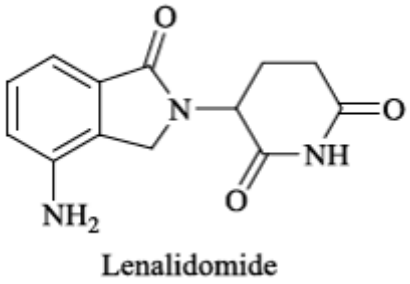
The product is available in PVC/PCTFE/Aluminium foil blister packs containing 7 hard capsules (2.5 mg, 7.5 mg, 20 mg, 25 mg), PVC/PCTFE/Aluminium foil blister packs containing 21 hard capsules (all

strengths) and PVC/PCTFE/Aluminium foil perforated unit dose blister packs containing 21 x 1 hard capsules (all strengths) 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-1,3-dihydro-1-oxo-2H-isoindol-2-yl)-2,6-piperidinedione corresponding to the molecular formula $C_{13}H_{13}N_3O_3$. It has a relative molecular mass of 259.27 g/mol and the following structure:



Lenalidomide

Figure 1: active substance structure

Lenalidomide is an off-white to pale yellow powder that is slightly hygroscopic. It is very slightly soluble in water (at 37°C) and slightly soluble across the physiological pH range (1.2 - 8.0).

The chemical structure of lenalidomide was elucidated by a combination of analytical techniques including IR, UV, 1H NMR, 13C NMR, Mass spectroscopy and Elemental analysis.

The solid-state properties of the active substance were measured by Powder X-ray diffraction (XRPD), Differential scanning calorimetry (DSC) and Thermo gravimetric analysis (TGA).

Lenalidomide has an asymmetric carbon atom and can therefore exist as the optically active forms R (-) and S (+). The active substance manufacturer consistently manufactures it as a racemic mixture. An optical rotation (1% w/v solution in dimethyl sulfoxide) study performed on three production scale batches of active substance confirms that the racemic mixture is consistently produced.

Lenalidomide exhibits polymorphism and can exist in seven crystalline and one amorphous polymorphic form. The active substance manufacturer consistently manufactures a single polymorphic form as confirmed by the data generated from testing of samples from representative batches. The tests for identification by XRPD and IR are routinely controlled in the active substance specification and at release and on stability.

Manufacture, characterisation and process controls

The active substance information is provided via an Active Substance Master File (ASMF) procedure. There is one ASMF Holder.

Lenalidomide is synthesised in five main steps using well defined starting materials with acceptable specifications. The detailed description of the manufacturing process of lenalidomide is provided in the Restricted Part of ASMF and it was considered satisfactory. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented and are acceptable.

During the procedure a major objection was raised relating to one of the proposed starting materials requesting further justification of its designation as starting material or for it to be redefined as an intermediate. The choice the starting material was subsequently justified by the applicant in line with the principles of ICH Q11 guideline. The detailed justification was provided in the updated Restricted Part of the ASMF.

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.

The applicant follows the ICH M7 Option 3 approach for controlling four identified potential genotoxic impurities based on the fact that they were not detected in three batches of active substance and are controlled earlier in the process in various intermediate specifications. In order to support this proposed approach, the applicant provided the results from relevant spiking studies. It was demonstrated that the proposed limits for these impurities in the intermediate specifications (e.g. 0.50 %w/w, 0.15 %w/w) are adequate to ensure that the impurities will always be <30% of the TTC (60 ppm) in the final active substance. The applicants control strategy for potential genotoxic impurities was therefore considered acceptable.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development programme. Sufficient details on the manufacturing process development have been provided in the Restricted Part of the ASMF.

The active substance is packaged in a polyethylene (LDPE) bag, twisted and tied with a plastic fastener. The polyethylene bag is then placed inside a triple laminated aluminium bag and the triple laminated aluminium bag is heat sealed. The triple laminated aluminium bag is further packed in HM-HDPE container, closed with plastic lid, sealed and labelled. The packaging materials comply with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for: description (visual), identification (IR, HPLC, XRPD), loss on drying (Ph. Eur.), sulfated ash (Ph. Eur.), related substances (HPLC), content of LEN-I (HPLC), assay (HPLC), residual solvents (HS-GC), dimethyl formamide (HPLC), palladium content (AAS/ICP-MS) and particle size (Malvern).

Appropriate specifications for impurities are set in line with the ICH Q3A guideline.

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

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

Stability

Stability data from eight production scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 60 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested: description, identification (HPLC, XRPD), loss on drying, related substances, content of LEN-I, assay. The analytical methods used were the same as for release and were stability.

All tested parameters were within the specifications and no trends were observed.

Photostability testing following the ICH guideline Q1B was performed on one batch. Results on stress conditions were also provide on one batch. The results obtained imply degradation by acid and base hydrolysis, oxidation and heat for the solution and no degradation by heat for the solid and light (white fluorescent light and an integrated UV light).

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 60 months with no special 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, 25 mg of lenalidomide. The appearance of the capsules is described below.

Lenalidomide 2.5 mg Capsules: A No.4, green opaque cap and white opaque body, hardshell gelatin capsule filled with white to off-white powder. The capsule is axially printed with **MYLAN** over **LL 2.5** in black ink on both cap and body.

Lenalidomide 5 mg Capsules: A No.2, white opaque cap and white opaque body, hardshell gelatin capsule filled with white to off-white powder. The capsule is axially printed with **MYLAN** over **LL 5** in black ink on both cap and body.

Lenalidomide 7.5 mg Capsules: A No.2, light gray opaque cap and white opaque body, hard-shell gelatin capsule filled with white to off-white powder. The capsule is axially printed with **MYLAN** over **LL 7.5** in black ink on both cap and body.

Lenalidomide 10 mg Capsules: A No.0, green opaque cap and light gray opaque body, hard-shell gelatin capsule filled with white to off-white powder. The capsule is axially printed with **MYLAN** over **LL 10** in black ink on both cap and body.

Lenalidomide 15 mg Capsules: A No.0, white opaque cap and white opaque body, hardshell gelatin capsule filled with white to off-white powder. The capsule is axially printed with **MYLAN** over **LL 15** in red ink on both cap and body.

Lenalidomide 20 mg Capsules: A No.0, green opaque cap and white opaque body, hardshell gelatin capsule filled with white to off-white powder. The capsule is axially printed with **MYLAN** over **LL 20** in red ink on both cap and body.

Lenalidomide 25 mg Capsules: A No.0, white opaque cap and white opaque body, hardshell gelatin capsule filled with white to off-white powder. The capsule is axially printed with **MYLAN** over **LL 25** in black ink on both cap and body.

The seven strengths of the finished product were designed into two dose-proportional groups with a separate common intermediate for each.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards, with the exception of iron oxides. 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 Quality Target Product Profile (QTPP) for finished product was defined based on the clinical and pharmacokinetic (PK) characteristics as well as the *in vitro* dissolution and physicochemical characteristics of the reference product (Revlimid) in order to achieve and demonstrate bioequivalence. Critical quality attributes (CQAs) were identified based on their direct impact on safety and efficacy and the fact that they are influenced by formulation and process variables. The choice of the assay, content uniformity, related compounds, dissolution as CQAs has been discussed and is considered acceptable.

The applicant has applied Quality by Design principles in the development of the finished product and the manufacturing process. However, no design spaces were claimed for the manufacturing process of the finished product. Risk assessment was used throughout development to identify potentially high-risk formulation and process variables, and to determine which studies were necessary to achieve product and process understanding in order to develop a control strategy. Each risk assessment was then updated after development to capture the reduced level of risk based on the improved product and process understanding.

The active substance attributes particle size distribution, chemical stability and flow properties were identified as those that could have an potential impact on the finished product CQAs The chosen formulation and process adequately mitigates these risks through the use of micronised active substance, compatible excipients, dry granulation and active substance-lubricant pre-blending steps.

The differences to qualitative composition of the finished product and the reference product (Revlimid) with respect to excipients are presented in the following table.

Table 1 Comparison of Excipients between Lenalidomide Mylan and Reference Product (Revlimid)

Mylan's Lenalidomide Capsules	Celgene's Revlimid® Capsules (Reference Drug) [1]	Functionality
Capsule Fill Components		
Starch, Pregelatinized	Lactose Anhydrous	Filler
Microcrystalline Cellulose	Microcrystalline Cellulose	Filler
Croscarmellose Sodium	Croscarmellose Sodium	Disintegrant
Silica, Colloidal Anhydrous [2]	N/A	Glidant
Sodium Stearyl Fumarate	Magnesium Stearate	Lubricant
Capsule Shell Components		
Gelatin	Gelatin	Shell forming component
Titanium Dioxide	Titanium Dioxide (E171)	Opacifying agent
Yellow Iron Oxide (2.5 mg, 7.5 mg, 10 mg and 20 mg only)	Yellow Iron Oxide (E172) (2.5 mg, 7.5 mg, 10 mg and 20 mg only)	Colorant
FD&C Blue No. 2 (2.5 mg, 10 mg and 20 mg only)	Indigo Carmine (E132) (2.5 mg, 10 mg, 15 mg and 20 mg only)	Colorant
Black Iron Oxide (7.5 mg, 10 mg only)	N/A	Colorant
Black Ink (all except 15 mg and 20 mg)	Black Ink	Imprinting Ink
Red Ink (15 mg and 20 mg only)	N/A	Imprinting Ink

A dry granulation process (including blend -> compaction -> mill -> blend -> final blend -> encapsulation steps) was selected for the manufacture of the finished product. For each unit operation that has medium to high risk for product critical quality attributes (CQAs), a risk assessment was conducted, and developmental studies were performed to investigate the identified high-risk variables to determine the critical material attributes (CMAs) and critical process parameters (CPPs). All process parameters (blending time and blender rotation rate) of Initial Blend Process are fixed and there are no process variables to investigate. The critical process parameters (CPPs) identified and monitored for the compaction/milling step were roll pressure and roll speed. The development studies indicated that the output material quality attributes are consistent in relatively wide critical process parameters (CPP) ranges. The final blending procedure and conditions (blending speed and time) have been shown to produce final blend at exhibit scale with acceptable final blend quality attributes. During the

encapsulation operation the risk is reduced to low as in-process capsule fill weights are tightly controlled. Among the attributes of the capsules, weight variation and dissolution are identified as the critical output material quality attributes. The effect of encapsulation pressure on active substance release was studied and the results indicated that encapsulation pressure has no effect on product dissolution.

The impurity profiles of the Lenalidomide Mylan finished product and the reference product were shown to be similar.

A bio-equivalence study was performed for lenalidomide 10 mg capsules and lenalidomide 25 mg capsules. There is no difference between the intended commercial formulation and those used during clinical studies. A change of color for 15 mg and 20 mg capsules was made during development.

There are no differences between the intended commercial process and the one used for the production of clinical batches used in bioequivalence studies.

Justification for selection of a dissolution medium and apparatus has been provided. Comparative dissolution profiles of the test product lenalidomide 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg and 25 mg capsules (manufactured by Mylan) and the European reference product Revlimid (lenalidomide) 10 mg and 25 mg capsules (Celgene Europe Limited, UK) were generated in different dissolution media i.e. QC release media, 0.1 N Hydrochloric acid, pH 4.5 Acetate buffer and pH 6.8 Phosphate buffer. It was observed that the release profile of test and reference formulation in QC release media, pH 4.5 acetate buffer and pH 6.8 phosphate buffer is not similar.

The difference in profile of the finished product may be attributed to changes in qualitative and quantitative composition and manufacturing process between test and reference products. However, the test product strengths 10 mg and 25 mg were shown to be bio-equivalent to the respective strengths of the reference product. Therefore, it can be concluded that the difference in active substance release profile does not have any impact on the *in-vivo* performance of the product.

In 0.1N HCl medium the dissolution profiles of test and reference formulations can be considered as similar based on guideline CPMP/EWP/QWP/1401/98-Rev 01. On the basis of the dose proportionality, similarity of dissolution among all the strengths of the test product and the established bioequivalence of the 10 mg and 25 mg strengths to Revlimid, a bioequivalence waiver was granted for the 2.5 mg, 5 mg, 7.5 mg, 15 mg and 20 mg strengths.

The discriminatory power of the QC dissolution method has been demonstrated.

The finished product is presented in PVC/PCTFE - Alu blister pack (marketable pack), while the bulk product is packed in Low-Density Polyethylene (LDPE) bag. The suitability of the selected packaging material is confirmed by the stability studies. The finished product manufacturer certificates of analysis compliance statements with the relevant EU Directives have been provided for all packaging components and are considered satisfactory.

Manufacture of the product and process controls

The manufacturing process consists of ten main steps: blending and sifting excipients, blending with lenalidomide, co-sifting, pre-compaction blending, compaction, blending of intermediate granules, blending with excipients, sifting, final blending, encapsulation, packaging.

The process is considered to be a standard manufacturing process. Although the active substance content of some capsules is approximately 2% of composition, if the capsule mass is taken into account, there is adequate prior knowledge and understanding of the manufacturing process to consider it standard.

The process description is considered comprehensive and a summary of the manufacturing conditions and operating parameters for the proposed commercial batch size is provided. The in-process controls 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. Process validation has been carried out by the finished product manufacturer for three batches of the two common blends at the proposed batch size. The encapsulation step for all strengths has been validated for the smallest proposed commercial batch size. Validation studies will be performed on the first three production-scale batches with the largest batch size and a process validation protocol/scheme are provided. The process validation scheme is based on the critical process parameters and critical quality attributes already discussed in the process validation of the small batch size batches and they are acceptable. 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 specifications include appropriate tests for this kind of dosage form: description/dimension (visual), identification (HPLC/PDA, HPLC), dissolution (Ph. Eur. / HPLC), uniformity of dosage units (Ph. Eur.), assay (HPLC), related compounds (HPLC), LEN 1 Impurity (HPLC), water (Ph. Eur.), microbiological test (Ph. Eur.) and colour identifications (in-house).

The finished product is released on the market based on the above specifications, through traditional final product release testing. The finished product specification tests and acceptance criteria are appropriately justified and considered to acceptable.

Based on a maximum daily dose of 25 mg, the ICH Q3B identification threshold is 0.2% and the qualification threshold is 0.5%. Hence, the limits for the unspecified and specified impurities are in accordance with the identification threshold. During the procedure, the dissolution limit has been tightened according to the reflection paper EMA/CHMP/CVMP/QWP/ 336031/2017. The release specification for water has also been tightened based on batch analysis results.

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.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. The assessment examined potential sources of elemental impurities and identified components that can introduce elemental impurities into the finished product. The theoretical evaluation showed that all Class I and 2A elements are well below the control threshold of 30% of PDE. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

A risk assessment for the presence of nitrosamines in the finished product was performed by the applicant applying principles outlined in the EMA notice "Information on nitrosamines for marketing authorisation holders". The applicant considered the formation of nitrosamines impurities in Lenalidomide 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg and 25 mg capsules through manufacturing process and packaging process (including packaging materials) and it was concluded that there is no known risk of nitrosamine impurity formation during these steps. For the manufacturing process, it was noted that there is no use of secondary amines, nitrous acid or its source or diethylamine. Hence, the possibility for the formation of nitrosamine impurities is ruled out. Also, it was noted that there are no recovered materials like recovered solvents, catalysts or reagents

used during the manufacturing process of the finished product. The risk assessment was considered to be adequately detailed and in line with the published guidance.

Batch analysis results are provided for multiple batches (including stability, process validation and production batches at commercial scale) confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from 22 batches of finished product stored for up to 12 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing (i.e. PVC/PCTFE/Alu blister pack). The data provided for each strength was as follows: for 2.5 mg (2 batches), 5mg (3 batches), 7.5 mg (3 batches), 10 mg (3 batches), 15 mg (4 batches), 20 mg (4 batches), 25 mg (3 batches).

Samples were tested for in line with the shelf life specifications. The analytical procedures used are stability indicating. It is noted that the results of the dissolution test at the 12-month interval of the stability study complied with the tighter acceptance limits agreed during the procedure.

There were no out of specification results observed at long term storage conditions. There was an increase trend in water content observed in 6 batches stored at accelerated conditions, however all remained within specification limits. An increase in the levels of impurity was observed at accelerated conditions.

A photostability study of lenalidomide 10 mg, 20 mg and 25 mg capsules conducted in line with ICH Q1B concluded that lenalidomide capsules are not photosensitive.

Forced degradation/stability indicating studies have been performed with samples of finished product subjected to environmental degradation conditions and samples of active substance subjected to environmental degradation conditions and solution phase degradation conditions. No degradation is observed to environmental degradation conditions. The active substance is significantly degraded in solution phase base degradation.

Based on available stability data, and taking account the ICH Q1E guideline, a shelf-life of 15 months (2.5 mg) and 24 months (5mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 25 mg) months with storage conditions "Do not store above 30°C" as stated in the SmPC (section 6.3 and 6.4) are considered acceptable.

Adventitious agents

Gelatine obtained from bovine sources is used in the product. Valid TSE CEP from the suppliers of the gelatine used in the manufacture is provided.

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.

A major objection on the choice of one starting material was sufficiently addressed by the applicant and the starting material was accepted in line with the principles of ICH Q11 guideline.

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.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.2.6. Recommendations 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 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

The applicant performed the Phase I of the ERA according to the ERA guideline (EMEA/CHMP/SWP/4447/00 corr 2).

Table 2. Summary of main study results

Substance (INN/Invented Name): Lenalidomide			
CAS-number (if available): 191732-72-6			
PBT screening		***Result***	***Conclusion***
Bioaccumulation potential- log K_{ow}	OECD107	Log Kow -0.4	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	Log Kow -0.4	not B
	BCF		not B
Persistence	DT50 or ready biodegradability		NA
Toxicity	NOEC or CMR		NA

PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC surfacewater , default or refined (e.g. prevalence, literature)	0.007	µg/L	> 0.01 threshold (N)
Other concerns (e.g. chemical class)			(N)

2.3.3. Discussion on non-clinical aspects

The non-clinical sections of the SmPC are acceptable and in accordance with those of the reference product. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is considered adequate.

Concerning Environmental Risk Assessment, the total PECSURFACEWATER value was determined at 0.007 µg/L, which is below the action limit of 0.01 µg/L. The applicant provided adequate justification based on European disease prevalence data, for each approved indication of lenalidomide, for the refinement of Fpen. Therefore, a Phase II assessment is not deemed necessary.

Data on an experimentally derived n-octanol/water partition coefficient (log Kow) for Lenalidomide Mylan were submitted by the applicant. The experimentally derived n-octanol/water partition coefficient (logKow) for Lenalidomide Mylan was found to be below the trigger of 4.5, indicating a low potential for bioaccumulation, comparable to the innovator. Thus, no increase in the environmental exposure is expected by the use of Lenalidomide Mylan.

2.3.4. Conclusion on the non-clinical aspects

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

2.4. Clinical aspects

2.4.1. Introduction

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

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

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

GCP

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

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

Exemption

In order to justify the biowaiver of strengths the applicant made reference to Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**) and Lenalidomide product-specific BE guidance *(*EMA/CHMP/177335/2016/Corr.)

The *in vivo* bioequivalence study for the strengths of 1) 2.5 and 5mg (10 mg series) and 2) 7.5, 15 and 20 mg (25mg series) can be waived as all biowaiver criteria are fulfilled. Specifically:

- Concerning PK linearity, the maximum concentration (Cmax) and area-under-the-concentration time curve (AUC) increase proportionally with increases in dose. Multiple dosing does not cause marked medicinal product accumulation.

- The pharmaceutical products are manufactured by the same manufacturing process.

- The qualitative composition of the different strengths is the same.

- The compositions of the strengths are quantitatively proportional.

In the case of the last criterion (similar in-vitro performance), the applicant has provided comparative dissolution data. Dissolution tests were conducted at different pH values 1.2, 4.5 and 6.8 between:

1) Lenalidomide Mylan 2.5 and 5mg tablets vs 10mg (batch used for the bioequivalence testing) and

2) Lenalidomide Mylan 7.5, 15 and 20 mg vs 25mg (batch used for the bioequivalence testing).

Comparative dissolution profiles of the test product Lenalidomide 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg and 25 mg Capsules (manufactured by Mylan) and the European reference product Revlimid (Lenalidomide) 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg and 25 mg Capsules (Celgene Europe Limited, UK) were generated in different dissolution media across the pH range of 1.2 to 6.8 including QC release media.

The release profile of all the stregnth of test formulation is found to be similar across the pH range of 1.2 to 6.8 More than 85% of the labeled amount of the drug is released within 15 minutes from all strengths of test product thus the dissolution profiles can be considered similar without further mathematical calculations.

<u>Test vs Reference product</u>

The applicant has also presented comparative dissolution profiles of the test product Lenalidomide Mylan 10 and 25 mg and the reference product Revlimid 10 and 25mg capsules of "Celgene Europe Limited, UK, performed in 0.1 N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer.

Based on the comparative dissolution profiles of the test product Lenalidomide Mylan 10 and 25 mg vs the reference product Revlimid 10 and 25mg capsules of "Celgene Europe Limited, UK, in 0.1 N HCl, pH4.5 acetate buffer and pH 6.8 phosphate buffer:

- more than 85% of the labelled amount of the drug is released within 15 minutes from the test formulation in pH 4.5 acetate buffer and pH 6.8 phosphate buffer whereas relatively slow release was observed for reference product

- more than 85% of the drug is released within 15 minutes in both the formulation in 0.1N- HCl.

Clinical studies

To support the application, the applicant has submitted 2 bioequivalence studies. A study on the 10 mg strength is used to support a bio waiver for the 2.5 mg and 5 mg strengths (referred to as the 10 mg series) and a study on the 25 mg strength is used to support a bio waiver for the 7.5 mg, 15 mg and 20 mg strengths (referred to as the 25 mg series).

Table 3. Tabular overview of clinical studies

Type of study	Study Identifier	Objectives of the study	Study design and Type of Control	Test product, Dosage Regimen Route of administration	Number of Subjects	Healthy Subjects or Diagnosis of patients	Duration of treatment	Study Status, Type of Report
BE	LENA-18009	To investigate the bioequivalence of Mylan's lenalidomide 25 mg capsules to Celgene's Revlimid 25 mg capsules following a single, oral 25 mg (1 x 25 mg) dose administration under fasting conditions.	A single-dose, randomised, two-period, two-treatment crossover study	Test product: Lenalidomide Mylan, capsules, 25 mg -a single oral dose of 25 mg (1 × 25 mg) Reference product: Revlimid capsules 25 mg -a single oral dose of 25 mg (1 × 25 mg).	Forty-eight (48) subjects were enrolled and dosed in the study, and forty-six (46) subjects completed the clinical portion of the study.	Healthy Adult Male Volunteers	Single dose	Completed
BE	LENA-18026	To investigate the bioequivalence of Mylan's lenalidomide 10 mg capsules to Celgene's Revlimid 10 mg capsules following a single, oral 10 mg (1 x 10 mg) dose administration under fasting conditions.	A single-dose, randomised, two-period, two-treatment crossover study	Test product: Lenalidomide Mylan, capsules, 10 mg -a single oral dose of 10 mg (1 × 10 mg) Reference product: Revlimid capsules 1mg -a single oral dose of 25 mg (1 × 10 mg).	A total of forty-eight (48) subjects were dosed in the study and forty-seven (47) subjects completed the clinical portion of the study.	Healthy Adult Male Volunteers	Single dose	Completed

2.4.2. Pharmacokinetics

Study LENA-18009: Single-Dose Fasting Bioequivalence Study of Lenalidomide Capsules (25 mg; Mylan) versus Revlimid Capsules (25 mg; Celgene) in Healthy Adult Male Volunteers

Methods

Study design

This was a single-dose, randomised, two-period, two-treatment crossover study investigating the bioequivalence of Mylan's lenalidomide capsules, 25 mg to Celgene's Revlimid capsules, 25 mg following administration of a single, oral dose in 48 healthy, adult male subjects under fasting conditions.

The study protocol dated 28-Mar-2018 was approved by IBIOME-IEC on 25-May-2018.

The objective of this study was to investigate the bioequivalence of Mylan's lenalidomide 25 mg capsules to Celgene's Revlimid 25 mg capsules following a single, oral 25 mg (1 x 25 mg) dose administration under fasting conditions.

The test and reference products were administered to the subjects according to the randomisation scheme.

The Study was conducted between 01/11/2018 (First subject treated) and 16/11/2018 (Last subject visit).

The study was initiated with forty-eight (48) healthy adult male subjects. On study day 1, each subject received either a single, oral dose of 25 mg (1 × 25 mg) of the test product, lenalidomide capsules, 25 mg or a single oral dose of 25 mg (1 × 25 mg) of the reference product, Revlimid capsules 25 mg. Dosing occurred following an overnight fast of at least 10 hours. There was a 3-day washout period between dosing times for the two treatment periods, after which all subjects were dosed with the alternative treatment as per the randomisation. In each study period, blood samples were collected within 120 minutes prior to dose administration (0 hour) and post-dose at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 14 and 16 hours. The subjects were allowed to leave the clinical facility 24 hours after Period 2 dosing.

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

According to the proposed dosing recommendations lenalidomide can be administered with or without food (Revlimid SmPC, 2019). Therefore, the performance of the BE study under fasting state is considered acceptable.

The wash out period of 3 days (more than 7 t1/2) used in the current study is adequate in order to ensure that no carry over effects might occur.

The sampling frequency can be considered adequate to provide a reliable estimate of Cmax based on the literature data for Tmax (0.5-3.00 hours) and confirmed by the observed Tmax values (range 0.5-3.0 hours for treatment A-test product and 0.5-2.5 hours for treatment B-Reference product).

Monitoring was long enough (16h, approx. 5 t1/2) to cover the plasma concentration-time curve and the sampling schedule provided a reliable estimate of the extent of exposure. AUC(0-t) covered at least 92% of AUC(0-∞) (AUCextrapolated <20%).

Test and reference products

The product characteristics for test and reference product are presented in the Table below:

Product Characteristics	Test Product	Reference Product
Name	Lenalidomide	Revlimid®
Strength	25 mg	25 mg
Dosage Form	Capsules	Capsules
Manufacturer	Mylan Laboratories Ltd.	Celgene Ltd.
Batch Number	2016057	A2526AE
Measured Content(s) (% of Label Claim)	102.9%	100.1%
Expiry Date (Retest Date)	09/2020	01/2020
Location of Certificate of Analysis	Section 3.2.P.5.4	Section 3.2.P.2
Member State where the reference product is purchased from:	Not Applicable	United Kingdom
This product was used in the following trials:	LENA-18009	LENA-18009

The certificates of analysis of the test and reference product were provided by the applicant (Assay: Test product 25 mg: 102.9% and Reference product 25 mg: 100.1%).

The biobatch size of the test product is acceptable according to the BE guideline.

Population(s) studied

Forty-eight (48) Asian subjects were enrolled and dosed in the study, and forty-six (46) subjects completed the clinical portion of the study.

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

The usual standard inclusion and exclusion criteria for bioequivalence studies were applied: healthy, non-tobacco/nicotine using, male volunteers 18-45 years old (inclusive), weighing at least 50 kg (110 lbs), with a Body Mass Index (BMI) less than or equal to 30 kg/m^2 but greater than or equal to 19 kg/m^2, who were judged to be healthy on the basis of a pre-study physical examination and clinical laboratory tests.

The study population chosen is appropriate and in line with current bioequivalence guideline. Population pharmacokinetic analyses indicate that body weight (33- 135 kg), gender, race and type of haematological malignancy (MM, MDS or MCL) do not have a clinically relevant effect on lenalidomide clearance in adult patients (Revlimid SmPC, 2019).

The protocol deviations included:

a) Blood sample collection time deviations for Subjects No 5, 10 and 31 (Treatment B-Revlimid) and

b) Plasma samples at pre-dose, 0.25, 0.5, 0.75, 1.0, 1.5, 2.0 and 2.5 hours post-dose in Period 1 for all subjects did not meet the storage criteria mentioned in the protocol (between -55°C to -90°C). Due to the frequent opening of the freezer to store plasma samples for the early blood sampling timepoints, the freezer temperature rose above -55°C (no higher than -50.75°C) for a short period of time (approx. 2-3 hours). Deviations in storage temperature were within the established stability; therefore, these deviations had no impact on the affected samples.

Analytical methods

The analytical portion of the bioequivalence study no. LENA-18009 was conducted at the Bioanalytical Laboratory of the CRC- Mylan Laboratories Ltd. in India, from 08th November 2018 to 13th November 2018 determining plasma lenalidomide concentrations in the clinical samples from Fasting Bioequivalence study.

The analysis was performed according to Analytical Method Procedure No. "AMP-206-00" and Study Protocol No. SP-LENA-18009 Version No.: 00 on three API 4000 LCMS/MS systems using lenalidomide 13C5 as an internal standard (IS) of the study. The interface used with the systems was a Turbo ionspray. The positive ions were measured in MRM mode.

Samples were collected via an indwelling catheter, inverted 5-10 times immediately after collection and immediately placed in an ice bath. The blood samples were placed in the centrifuge within 30 minutes from blood sample collection. The samples were then centrifuged at 1900g ± 400g (e.g. 3000 rpm for 19 cm rotor radius) for 10 minutes under refrigeration (4°C ± 3°C). The plasma was returned to an ice bath and transferred into the following labelled polypropylene tubes: SARSTEDT, Inc., Cat. No.: 60.542, Description: 8 mL PP with cap.

Each plasma sample was divided equally into two (2) aliquots. Transfer of the samples into the freezer took place no later than 90 minutes after the start of centrifugation. The plasma samples were maintained in an ice bath until transfer to the storage freezer occurred. Samples were frozen in an upright position at -70°C with an acceptable operating range within -55°C to -90°C.

The details of the collected and analysed samples are described in the following Tables.

Date of Dosing (Period-I)	01st November 2018
Clinical site	Cliantha Research Limited, Ahmedabad
Study Samples received date	06th November 2018
Storage condition at clinical site	At set temperature -70°C
Samples condition during Transit	Frozen and intact
Deviations any during Transit	No significant deviations found during transit
Storage condition at bioanalytical site until sample analysis	At set temperature -70°C
Total number of samples received	1601
Number of Subjects completed the study	46 subjects out of 48 subjects
Date of analysis started	08th November 2018
Date of analysis completed	13th November 2018

Number of sample collected in each period	17 (0.00 to 16.00 Hrs)
Number of expected samples in two periods	1632 (48 x 2 x 17)
No. of Drop Out (Subjects)	02 Subjects (Sub 29 & 31)
Number of samples received	1601 (1632-31)
Total number of missing samples	31 samples S29: PII (0.75 to 16.00 Hrs) = 14 samples S31: PII (0.00 to 16.00 Hrs) = 17 samples
Number of Subject samples analyzed	1564 From 46 evaluable subjects

The method developed for the analysis of lenalidomide in 100 µL K2EDTA human plasma was performed using ultra high-performance liquid chromatography with tandem mass spectroscopy. The lower limit of quantitation (LLOQ) was 2.010 ng/mL and the upper limit of quantitation (ULOQ) was 803.953ng/mL.

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

Chromatograms have been presented by the applicant in the LENA-18009 Bioanalytical Study Report for standard curve concentration levels, quality control concentrations and unknown blood sample assays for subject numbers 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12.

Validation of the test method

The applicant has provided the validation report of the test method (VR-2016, Version 00). Specifically, the method validation characteristics that were addressed were: Specificity, Selectivity, Carry Over effects, Linearity, % Recovery of Analyte and Internal Standard, Matrix effect, Precision and accuracy as well as stability.

Analytes	Lenalidomide
Total Number of incurred samples analyzed	184
Total Number of samples considered for Incurred Samples Reanalysis Calculation	184
Total Number of samples met acceptance criteria	184
Total % of samples within the acceptance range	100.00

There was no re-injection or re-integration in this study.

All the subject samples with reported final results showed acceptable chromatograms.

The Analytical method used for the lenalidomide concentration in plasma determination seems to be adequately presented and to follow the requirements of the "Guideline on Bioanalytical method validation" (EMEA/CHMP/EWP/192217/09 Rev.1/Corr. 2**).

Concerning Specificity, Selectivity and Injection Carry Over effect no significant interferences at tested matrices were observed for Lenalidomide and Internal Standard (Lenalidomide 13C5), while the Limit

of Quantification (2.010 ng/mL) was adequate to quantify low concentration samples.

The longest storage period prior analysis was 13 days at -70°C for Lena-18009. Long term stability was determined for a sufficient time period of 66 days at -70°C.

The applicant has submitted a bioanalytical report presenting the bioanalysis results of the bioequivalence study. The total number of collected samples was 1601 and total number of analysed samples with valid results was 1564 (from 46 evaluable subjects). Incurred sample reanalysis was performed on 184 samples. 100% of samples were within specifications regarding %Difference (repeat-original) with differences between the two values less than 20% of the mean for chromatographic assays.

Pharmacokinetic variables

Single-dose pharmacokinetic parameters for lenalidomide were calculated using non-compartmental techniques.

The maximum concentration (C_{max}) and the time at which it occurred relative to the administered dose (T_{max}) was determined from the observed plasma concentration-time profile over the sampling time interval.

The elimination rate constant (K_{el}) was determined by linear regression of the terminal linear phase of the log plasma concentration-time profile.

Area under the plasma concentration-time curve (AUC_{0-t}) is the sum of the linear trapezoidal estimation of the areas from the time of dosing to the time of the last quantifiable concentration.

Area under the plasma concentration-time curve from zero to infinity (AUC_{0-inf}) was calculated as: $AUC_{0-inf} = AUC_{0-t} + LQC/K_{el}$ where LQC is the last quantifiable concentration.

The elimination half-life ($t_{1/2}$) was calculated as $t_{1/2} = 0.693/K_{el}$.

The pharmacokinetic parameters Cmax and AUC_{0-t} (primary pharmacokinetic parameters) as well as T_{max}, K_{el}, $t_{1/2}$, and AUC_{0-inf} were computed using non-compartmental model for Lenalidomide of test product (T) and reference product (R).

An internally validated SAS program to calculate non-compartmental PK parameters, including automatic K_{el} selection was used. Both the K_{el} selection and PK parameter calculation SAS programs were validated in Oct 2012 under SAS 9.3 TS for unix AIX server. The SAS macro program validation reports have been provided for both K_{el} and PK parameters.

The pharmacokinetic variables chosen for demonstration of bioequivalence are appropriate.

Statistical methods

Statistical analyses were performed on the pharmacokinetic parameters using the General Linear Models Procedure (PROC GLM) of SAS Software (SAS Institute, Cary, NC). The model tested for treatment effects in the parameter means at an alpha level of 0.05.

The parameters: T_{max}, K_{el} and $t_{1/2}$ were analysed statistically using the non-transformed data. The natural log transformed parameters: $LNAUC_{0-t}$, $LNAUC_{0-\infty}$ and LNC_{max} were also analysed. The tests were performed to analyse for statistically significant differences in the pharmacokinetic parameters and to determine the test to reference ratios of the pharmacokinetic parameters using Least Squares Means. Ninety (90%) percent confidence intervals were constructed using the two one-sided tests procedure.

The 90% confidence interval for the LSMeans ratio of Cmax, AUC_{0-t}, and $AUC_{0-\infty}$ for the test and reference product should be between 80.00% and 125.00% for the natural log-transformed data.

Selection of PK parameters, statistical evaluation of the PK parameters and the acceptance ranges for bioequivalence are in accordance with the bioequivalence guideline (CPMP/EWP/QWP/1401/98 Rev.1 Cor**).

The SAS proc glm was used to calculate sequence and period effects. In SAS language software, the proc glm uses F-test in ANOVA model to determine the p values.

Results

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

Pharmacokinetic parameter	Test		Reference	
	Arithmetic Mean	**CV%**	**arithmetic mean**	**CV%**
$AUC_{(0-t)}$ (ng*hr/ml)	2005	17.18	1905	19.14
$AUC_{(0-\infty)}$ (ng*hr/ml)	2074	18.18	1973	20.10
C_{max} (ng/ml)	536.9	21.66	476.5	20.01
T_{max}* (hr)	0.826	36.02	0.973	36.44

AUC_{0-t} : area under the plasma concentration-time curve from time zero to t hours;
$AUC_{0-\infty}$: area under the plasma concentration-time curve from time zero to infinity;
C_{max} : maximum plasma concentration;
T_{max} : time for maximum concentration (* median, range)

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

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*	Power %
$AUC_{(0-t)}$ **(ng*hr/ml)**	1.06	104.42%-107.17%	3.70	>99.00
$AUC_{(0-\infty)}$ **(ng*hr/ml)**	1.06	104.30%-107.10%	3.78	>99.00
C_{max} **(ng/ml)**	1.13	106.96%-119.14%	15.47	93.08

* estimated from the Residual Mean Squares

The results showed that the ratios of the geometric least square mean of ln-transformed data (test/reference) for ln AUC_{0-t} and ln C_{max} were within the acceptable BE range (80.00%-125.00%).

Safety data

Three (3) post-dose adverse events were experienced by three (3) subjects over the course of this Study. The AEs were mild in severity. No serious adverse events (SAEs) were reported.

None of the AEs reported can be definitively attributed to Treatment A (test product) or Treatment B (reference product) since clinical labs were only evaluated at Screening and Study Exit.

No deaths, other serious adverse events, or other significant adverse events occurred over the course of the study.

All results concerning the laboratory measurements were reviewed by the clinical investigators. Values outside the reported reference range were either designated as not clinically significant (NCS) or follow-up testing was required.

Blood and urine samples were collected at the screening visit for clinical laboratory evaluations (haematology, biochemistry, urinalysis, serology, urine cotinine test, urine drug screen). Laboratory tests (chemistries, haematology or urine) were repeated as needed at the discretion of the investigator

for subjects whose test values were out of range but not clinically significant. The screening clinical laboratory results were reviewed and approved for subject enrolment by the clinical investigators prior to Period 1 dose administration.

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

Overall, lenalidomide was well tolerated as a single, oral 25 mg (1 x 25 mg capsule) dose administered under fasting conditions. Both products were found to be safe and well tolerated.

***Study LENA-18026*:** Single-Dose Fasting Bioequivalence Study of Lenalidomide Capsules (10 mg; Mylan) versus Revlimid Capsules (10 mg; Celgene) in Healthy Adult Male Volunteers

Methods

Study design

This was a single-dose, randomised, two-period, two-treatment crossover study investigating the bioequivalence of Mylan's lenalidomide capsules, 10 mg to Celgene's Revlimid capsules, 10 mg following administration of a single, oral dose in 48 healthy, adult male subjects under fasting conditions.

The objective of this study was to investigate the bioequivalence of Mylan's lenalidomide 10 mg capsules to Celgene's Revlimid 10 mg capsules following a single, oral 10 mg (1 × 10 mg) dose administration under fasting conditions.

The test and reference products were administered to the subjects according to the randomisation scheme.

The Study was conducted between 12/03/2019 (First subject treated) and 03/04/2019 (Last subject visit).

The study was initiated with forty-eight (48) healthy adult male Asian subjects. On study day 1, each subject received either a single, oral dose of 10 mg (1 × 10 mg) of the test product, lenalidomide capsules, 10 mg or a single oral dose of 10 mg (1 × 10 mg) of the reference product, Revlimid capsules 10 mg. Dosing occurred following an overnight fast of at least 10 hours. There was a 3-day washout period between dosing times for the two treatment periods, after which all subjects were dosed with the alternative treatment as per the randomisation. In each study period, blood samples were collected within 120 minutes prior to dose administration (0 hour) and post-dose at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 14 and 16 hours. The subjects were allowed to leave the clinical facility 24 hours after Period 2 dosing.

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

The Bioequivalence study was conducted under fasting conditions which is in accordance with the proposed dosing recommendations (Revlimid SmPC, 2019). Therefore, the performance of the BE study under fasting state is considered acceptable.

As noted above for the Lena-18009 BE the wash out period of 3 days used also in the current study is adequate in order to ensure that no carry over effects might occur.

The sampling frequency can be considered adequate to provide a reliable estimate of C_{max} based on the literature data for T_{max} (0.5-3.00 hours) and confirmed by the observed T_{max} values (range 0.5-3.0 hours for treatment A -test product and 0.5-2.5 hours for treatment B-Reference product).

Monitoring was long enough (16h, approx. 5 $t_{1/2}$) to cover the plasma concentration-time curve and the sampling schedule provided a reliable estimate of the extent of exposure. $AUC_{(0-t)}$ covered at least 92% of $AUC_{(0-\infty)}$ ($AUC_{extrapolated}$ <20%).

Test and reference products

The product characteristics for test and reference product are presented in the Table below:

Product Characteristics	**Test Product**	**Reference Product**
Name	Lenalidomide	Revlimid®
Strength	10 mg	10 mg
Dosage Form	Capsules	Capsules
Manufacturer	Mylan Laboratories Ltd.	Celgene Ltd.
Batch Number	2016486	A2501AI
Measured content(s) (% of Label Claim)	101.4%	99.7%
Expiry Date (Retest Date)	12/2020	11/2019
Location of Certificate of Analysis	Section 3.2.P.5.4	Section 3.2.P.2
Member State where the reference product is purchased from:	Not Applicable	United Kingdom
This product was used in the following trials:	LENA-18026	LENA-18026

The certificates of analysis of the test and reference product were provided by the applicant (Assay: Test product 10 mg: 101.4% and Reference product 10 mg: 99.7%).

The biobatch size of the test product is acceptable according to the BE guideline.

Population(s) studied

A total of forty-eight (48) Asian subjects were dosed in the study. Subject 18 withdrew consent due to personal reasons prior to Period 2 dosing. Therefore, forty-seven (47) subjects completed the clinical portion of the study and are included in the pharmacokinetic analysis.

The sample size calculation is considered acceptable.

Inclusion criteria: Healthy, non-tobacco/nicotine using, male volunteers 18-45 years old (inclusive), weighing at least 50 kg (110 lbs), with a Body Mass Index (BMI) less than or equal to 30 kg/m2 but greater than or equal to 19 kg/m2, who were judged to be healthy on the basis of a pre-study physical examination and clinical laboratory tests.

The inclusion and exclusion criteria are considered adequate, appropriate and standard for such bioequivalence studies since they follow the BE Guideline.

The study population chosen is appropriate and in line with current bioequivalence guidance. Population pharmacokinetic analyses indicate that body weight (33- 135 kg), gender, race and type of haematological malignancy (MM, MDS or MCL) do not have a clinically relevant effect on lenalidomide clearance in adult patients (Revlimid SmPC, 2019).

Protocol deviations

The protocol deviations included:

a) Blood sample collection time deviations for Subject No 30 (Treatment A) and Subjects No 25, 30 and 40 (Treatment B) and

b) Subjects No 44, 45 and 48 (Treatment A) and No 46, 47 (Treatment B): A standard low-fat meal was not provided per protocol the evening prior to dosing as subjects had consumed their last meal prior to reporting to the clinical facility.

The protocol deviations presented by the applicant are not expected to have an impact on the results of the study.

Analytical methods

The analytical portion of the bioequivalence Study No. LENA-18026 was conducted at the Bioanalytical Laboratory of the CRC- Mylan Laboratories Ltd. Dr. A.S. Rao Nagar, Hyderabad-500062, India, from 19th March 2019 to 25th March 2019 determining plasma Lenalidomide concentrations in the clinical samples from Fasting Bioequivalence study.

The analysis was performed according to Analytical Method Procedure No. "AMP-206-00" and Study Protocol No. SP-LENA-18026 Version No.: 1.0 on API 4000 LCMS/MS and Waters Xevo TQ MS system using Lenalidomide 13C5 as an internal standard (IS) of the study. The interface used with the systems was a Turbo ionspray. The positive ions were measured in MRM mode.

Samples were collected via an indwelling catheter, inverted 5-10 times immediately after collection and immediately placed in an ice bath. The blood samples were placed in the centrifuge within 30 minutes from blood sample collection. The samples were then centrifuged at 1900g ± 400g (e.g. 3000 rpm for 19 cm rotor radius) for 10 minutes under refrigeration (4±3^{o}C). The plasma was returned to an ice bath and transferred into the following labeled polypropylene tubes: SARSTEDT, Inc., Cat. No.: 60.542, Description: 8 mL PP with cap.

Each plasma sample was divided equally into two (2) aliquots. Transfer of the samples into the freezer took place no later than 90 minutes after the start of centrifugation. The plasma samples were maintained in an ice bath until transfer to the storage freezer occurred. Samples were frozen in an upright position at -70^{o}C with an acceptable operating range within -55°C to -90^{o}C.

Upon completion of the study, the plasma samples were shipped to the bioanalytical laboratory (Aliquot 1 on 16-Mar-2019) and received at Mylan Laboratories Ltd., Hyderabad, India for analysis. Aliquot 2

plasma samples were retained at Cliantha until instructed to be destroyed by Mylan Laboratories Ltd. on 05-Jun-2019.

Information regarding the time span between blood sampling and freezing samples in not specified as in LENA -18009 BE study, indicated as protocol deviation.

The details of the analysed samples are described in the Tables below.

Date of Dosing (Period-I)	12th March 2019
Clinical site	Cliantha Research Limited, Ahmedabad
Study Samples received date	18th March 2019
Storage condition at clinical site	At set temperature -70°C
Samples condition during Transit	Frozen and intact
Storage condition at bioanalytical site until sample analysis	At set temperature -70°C
Total number of samples received	1615
Number of Subjects completed the study	47 subjects out of 48 subjects
Date of analysis started	19th March 2019
Date of analysis completed	25th March 2019

Number of sample collected in each period	17 (0.00 to 16.00 Hrs)
Number of expected samples in two periods	1632 (48 x 2 x 17)
No. of Drop Out (Subjects)	01 Subject (Sub 18)
Number of samples received	1615 (1632-17)
Total number of missing samples	17 samples S18: PII (0.00 to 16.00 Hrs) = 17 samples
Number of Subject samples analyzed	1598 From 47 evaluable subjects

The assay for lenalidomide was linear from 2.000 ng/mL to 399.908 ng/mL. The method developed for the analysis of lenalidomide in 100 µL K2EDTA human plasma was performed using ultra high-performance liquid chromatography with tandem mass spectroscopy, which had a limit of quantification of 2.010 ng/mL.

Chromatograms have been presented by the applicant in the LENA-18026 Bioanalytical Study Report for standard curve concentration levels, quality control concentrations and unknown blood sample assays for subject numbers 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12.

Validation of the test method

The applicant has submitted the validation report and the respective results are presented in the LENA -18009 study.

The Analytical method used for the lenalidomide concentration in plasma determination seems to be adequately presented and to follow the requirements of the "Guideline on Bioanalytical method validation" (EMEA/CHMP/EWP/192217/09 Rev.1/Corr. 2**) (See Relevant Section for LENA-18009).

The longest storage period prior analysis was 14 days at -70°C for Lena-18026. Long term stability was determined for a sufficient time period of 66 days at -70°C.

The applicant has submitted a bioanalytical report presenting the bioanalysis results of the bioequivalence study. The total number of collected samples was 1615 and total number of analysed samples with valid results was 1598. Incurred sample reanalysis was performed on 157 samples. 100% of samples were within specifications regarding %Difference (repeat-original) with differences between the two values less than 20% of the mean for chromatographic assays.

Pharmacokinetic variables

Single-dose pharmacokinetic parameters for lenalidomide were calculated using non-compartmental techniques.

The maximum concentration (C_{max}) and the time at which it occurred relative to the administered dose (T_{max}) was determined from the observed plasma concentration-time profile over the sampling time interval.

The elimination rate constant (K_{el}) was determined by linear regression of the terminal linear phase of the log plasma concentration-time profile.

Area under the plasma concentration-time curve (AUC_{0-t}) is the sum of the linear trapezoidal estimation of the areas from the time of dosing to the time of the last quantifiable concentration.

Area under the plasma concentration-time curve from zero to infinity (AUC_{0-inf}) was calculated as: $AUC_{0-inf} = AUC_{0-t} + LQC/K_{el}$ where LQC is the last quantifiable concentration.

The elimination half-life ($t_{1/2}$) was calculated as $t_{1/2} = 0.693/K_{el}$.

The pharmacokinetic parameters C_{max} and AUC_{0-t} (primary pharmacokinetic parameters) as well as T_{max}, K_{el}, $t_{1/2}$, and AUC_{0-inf} were computed using non-compartmental model for Lenalidomide of test product (T) and reference product (R).

An internally validated SAS program to calculate non-compartmental PK parameters, including automatic K_{el} selection was used. Both the K_{el} selection and PK parameter calculation SAS programs were validated in Oct 2012 under SAS 9.3 TS for unix AIX server. The SAS macro program validation reports have been provided for both K_{el} and PK parameters.

The pharmacokinetic variables chosen for demonstration of bioequivalence are appropriate.

Statistical methods

Statistical analyses were performed on the pharmacokinetic parameters using the General Linear Models Procedure (PROC GLM) of SAS Software (SAS Institute, Cary, NC). The model tested for treatment effects in the parameter means at an alpha level of 0.05. The parameters: Tmax, K_{el} and $t_{1/2}$ were analysed statistically using the non-transformed data. The natural log transformed parameters: $LNAUC_{0-t}$, $LNAUC_{0-inf}$ and LNC_{max} were also analysed. The tests were performed to analyse for statistically significant differences in the pharmacokinetic parameters and to determine the test to reference ratios of the pharmacokinetic parameters using Least Squares Means. Ninety (90%) percent confidence intervals were constructed using the two one-sided tests procedure.

The determination of biologically implausible (pharmacokinetic) outliers and the statistical method used to identify statistical outliers are prescribed in the Study protocol (see relevant section for BE Lena-18009).

The 90% confidence interval for the LSMeans ratio of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ for the test and reference product should be between 80.00% and 125.00% for the natural log-transformed data.

Selection of PK parameters, statistical evaluation of the PK parameters and the acceptance ranges for bioequivalence are in accordance with the bioequivalence guideline (CPMP/EWP/QWP/1401/98 Rev.1 Cor**). The 90% confidence interval for the LSMeans ratio of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ for the test and reference product was calculated in order to assess bioequivalence.

The statistical methods chosen are considered appropriate. The SAS proc glm was used to calculate sequence and period effects. In SAS language software, the proc glm uses F-test in ANOVA model to determine the p values.

Results

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

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}	47	210.491	45.519	136.305	209.830	323.337	21.625
$AUC_{(0-t)}$	47	741.876	117.591	491.704	747.776	924.294	15.850
$AUC_{(0-\infty)}$	47	764.127	125.340	502.592	771.556	967.554	16.403
AUC_{ratio} (%)	47	97.18	1.08	92.79	97.27	98.63	1.11
T_{max}	47	0.846	0.438	0.500	0.750	3.000	51.772
$t_{1/2}$	47	3.136	0.368	2.518	3.085	4.136	11.749
K_{el}	47	0.2239	0.0258	0.1676	0.2247	0.2753	11.5237

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}	47	186.539	41.149	94.223	191.597	266.441	22.059
$AUC_{(0-t)}$	47	713.412	115.180	482.998	751.508	910.469	16.145
$AUC_{(0-\infty)}$	47	736.350	122.288	492.660	775.317	930.463	16.607
AUC_{ratio} (%)	47	96.97	1.12	93.36	96.95	98.51	1.15
T_{max}	47	1.021	0.426	0.500	1.000	2.500	41.727
$t_{1/2}$	47	3.156	0.414	2.345	3.178	4.005	13.119
K_{el}	47	0.2234	0.0294	0.1731	0.2181	0.2955	13.1596

Table 8. Mean (%CV) Lenalidomide Pharmacokinetic Parameters in Forty-Seven Healthy Adult Male Subjects Following a Single, Oral 10 mg Dose Administered Under Fasting Conditions (Non-transformed values)

Pharmacokinetic parameter	Test		Reference	
	Arithmetic Mean	CV%	arithmetic mean	CV%
$AUC_{(0-t)}$ (ng*hr/ml)	741.9	15.85	1905	19.14
$AUC_{(0-\infty)}$ (ng*hr/ml)	764.1	16.40	1973	20.10
C_{max} (ng/ml)	210.5	21.63	186.5	22.06
T_{max}* (hr)	0.846	51.77	1.021	41.73
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours>			
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity			
C_{max}	maximum plasma concentration			
T_{max}	time for maximum concentration (* median, range)			

Table 9. Mean (%CV) Lenalidomide Pharmacokinetic Parameters in Forty-Seven Healthy Adult Male Subjects Following a Single, Oral 10 mg Dose Administered Under Fasting Conditions (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*	Power %
$AUC_{(0-t)}$ (ng*hr/ml)	1.04	101.91%–105.93%	5.60	>99.00
$AUC_{(0-t)}$ (ng*hr/ml)	1.04	102.11%-106.18%	5.65	>99.00
C_{max} (ng/ml)	1.13	106.57%-120.85%	18.30	81.49
* estimated from the Residual Mean Squares				

Statistical analyses of these data reveal that the 90% confidence intervals are within the acceptable bioequivalent range of 80.00% and 125.00% for the natural log transformed parameters, $LNAUC_{0-t}$, $LNAUC_{0-inf}$ and LNC_{max} for lenalidomide. This study demonstrates that Mylan's lenalidomide capsules, 10 mg are bioequivalent to Celgene's Revlimid Capsules, 10 mg following administration of a single, oral 10 mg (1 x 10 mg) dose under fasting conditions.

Safety data

Six (6) post-dose adverse events were experienced by five (5) subjects over the course of this study. There were four (4) AEs (eosinophil count increased (2), alanine aminotransferase increased, aspartate aminotransferase increased) that were considered possibly related to study drug administration and two (2) AEs (blood cholesterol increased, white blood cell count increased) which were considered unlikely related to study drug administration.

The AEs were mild in severity. No serious adverse events (SAEs) were reported.

None of the AEs reported can be definitively attributed to Treatment A (test product) or Treatment B (reference product) since clinical labs were only evaluated at Screening and Study Exit.

No deaths, other serious adverse events, or other significant adverse events occurred over the course of the study.

All results concerning the laboratory measurements were reviewed by the clinical investigators. Values outside the reported reference range were either designated as not clinically significant (NCS) or follow-up testing was required.

Blood and urine samples were collected at the screening visit for clinical laboratory evaluations (haematology, biochemistry, urinalysis, serology, urine cotinine test, urine drug screen). Laboratory tests (chemistries, haematology or urine) were repeated as needed at the discretion of the investigator

for subjects whose test values were out of range but not clinically significant. The screening clinical laboratory results were reviewed and approved for subject enrolment by the clinical investigators prior to Period 1 dose administration.

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

Overall, lenalidomide was well tolerated as a single, oral 10 mg (1 x 10 mg capsule) dose administered under fasting conditions. Both products were safe and well tolerated.

Conclusions

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

The results of study LENA-18009 with 25 mg formulation can be extrapolated to other strengths 7.5, 15 and 20 mg, according to conditions in the Guidelines.

The results of study LENA-18026 with 10 mg formulation can be extrapolated to other strengths 2.5, 5 and 10 mg, according to conditions in the Guidelines.

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 applicant has submitted two bioequivalence studies (LENA-18009 and LENA-18026) which have been carried out with the strengths of 25 and 10mg, respectively. The BE study on the 10 mg strength was used to support a biowaiver for the 2.5 mg and 5 mg strengths (10mg series) and the study on the 25 mg strength was used to support a biowaiver for the 7.5 mg, 15 mg and 20 mg strengths (25mg series).

With regard to the bioequivalence studies submitted by the applicant the study design, study population, selection of PK parameters, determination of sample size, statistical evaluation of the PK parameters as well as the acceptance ranges for bioequivalence are in accordance with the bioequivalence guideline (CPMP/EWP/QWP/1401/98 Rev.1 Cor**).

The analytical method used for the lenalidomide concentration in plasma determination for both BE studies seems to be adequately presented and to follow the requirements of the "Guideline on Bionalytical method validation" (EMEA/CHMP/EWP/192217/09). The applicant has performed the standard validations for the analytical method.

The pharmacokinetic parameters Cmax and AUC_{0-t} (primary pharmacokinetic parameters) as well as T_{max}, K_{el}, $t_{1/2}$, and AUC_{0-inf} for both BE studies were computed using non-compartmental model for Lenalidomide of test product (T) and reference product (R). An internally validated SAS program was

used to calculate non-compartmental PK parameters, including automatic k_{el} selection. Both the k_{el} selection and PK parameter calculation SAS programs were validated in Oct 2012 under SAS 9.3 TS for unix AIX server. The SAS macro program validation reports are provided for both k_{el} and PK parameters.

The results of both studies (LENA-18009 and LENA-18026) showed that the ratios of the geometric least square mean of ln-transformed data (test/reference) for ln AUC_{0-t} and ln C_{max} were within the acceptable BE range (80.00%-125.00%).

The statistical methods chosen are considered appropriate. The SAS proc glm was used to calculate sequence and period effects. In SAS language software, the proc glm uses F-test in ANOVA model to determine the p values.

During review, the applicant was requested to discuss the statistical significance of formulation/treatment, sequence and period effects shown in the relevant ANOVA tables.

According to the applicant's response, the possible reasons for a period or treatment significant effect could be due to small/low variability of the PK parameters and/or large sample size. When the intra-subject CV is small and sample size is large, even a small period or treatment difference would become significant. However, the SAS GLM Procedure model utilised for analysis adjusts the period effects when it estimates treatment effect. Thus, the results presented in the submitted report took any period significant effects into account and adjusted for them in the statistical model utilised for determination of treatment effect. The treatment effect can be statistically significant, but when the 90% CI is within 80-125, the test product can still be considered as equivalent to the Reference product. Thus, based on the above the applicant did not anticipate any sequence effect on any PK parameters. The protocol deviations presented by the applicant are not expected to have an impact of the results of the study.

With regard to the safety data, the two formulations were well tolerated, with no apparent differences in safety profiles.

Biowaiver of Strengths

The *in vivo* bioequivalence study for the strengths of 1) 2.5 and 5mg (10 mg series) and 2) 7.5, 15 and 20 mg (25mg series) can be waived as all biowaiver of strength criteria are fulfilled.

In the case of criterion (d) (similar in-vitro performance), the applicant has provided comparative dissolution data and the dissolution profiles can be considered similar.

2.4.6. Conclusions on clinical aspects

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

Lenalidomide Mylan 10 mg and 25mg can be considered bioequivalent with the originator product Revlimid 10 mg and 25mg (Celgene Europe Limited, UK), respectively.

The results of study LENA-18009 with Lenalidomide Mylan 25mg can be extrapolated to the strengths 2.5 and 5 mg and the results of LENA-18026 with Lenalidomide Mylan 10 mg can be extrapolated to the strengths 7.5, 15 and 20 mg, as in both cases the biowaiver of strength criteria are fulfilled.

2.5. Risk management plan

Safety concerns

Summary of safety concerns	
Important identified risks	• Teratogenicity • Serious infection due to neutropenia • Second primary malignancies (SPM) Important Identified Risk Related to Indication/Target Population: • For FL (follicular lymphoma): TFR
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	Due Dates
Pregnancy Prevention Programme	Monitoring of implementation and effectiveness of the PPP	Teratogenicity	Routine PSURs in line with EURD list	In line with DLP of the latest EURD list

Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Teratogenicity	Routine risk minimisation measures Additional risk minimisation measures: • Pregnancy prevention programme • HCP and Patient educational materials • Patient card	Routine pharmacovigilance activities Additional pharmacovigilance activities: None
Serious infection due to neutropenia	Routine risk minimisation measures Additional risk minimisation measures: None	Routine pharmacovigilance activities Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Second Primary Malignancies	Routine risk minimisation measures Additional risk minimisation measures: HCP and patient educational materials	Routine pharmacovigilance activities Additional pharmacovigilance activities: None
For FL (follicular lymphoma): TFR	Routine risk minimisation measures Additional risk minimisation measures: HCP educational material	Routine pharmacovigilance activities Additional pharmacovigilance activities: None
Cardiac failure	Routine risk minimisation measures Additional risk minimisation measures: None	Routine pharmacovigilance activities Additional pharmacovigilance activities: None
Cardiac arrhythmias	Routine risk minimisation measures Additional risk minimisation measures: None	Routine pharmacovigilance activities Additional pharmacovigilance activities: None
Ischaemic heart disease (including myocardial infarction)	Routine risk minimisation measures Additional risk minimisation measures: None	Routine pharmacovigilance activities Additional pharmacovigilance activities: None
Off- label use	Routine risk minimisation measures Additional risk minimisation measures: None	Routine pharmacovigilance activities Additional pharmacovigilance activities: None

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.6 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 Duloxetine Mylan 30 mg hard gastro-resistant capsules package information leaflet for visual presentation and Revlimid 2.5mg, 5mg, 7.5mg, 10mg, 15mg, 20mg, 25mg hard capsules package information leaflet for content.

3. Benefit-risk balance

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

Multiple myeloma

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

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

- 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

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

Mantle cell lymphoma

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

Follicular lymphoma

- in combination with rituximab (anti-CD20 antibody) is indicated for the treatment of adult patients

with previously treated follicular lymphoma (Grade 1 – 3a).

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

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

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

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

4. Recommendation

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

Multiple myeloma

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

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

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

Follicular lymphoma

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

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

Conditions or restrictions regarding supply and use

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

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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

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

Risk Management Plan (RMP)

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

An updated RMP should be submitted:

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

Additional risk minimisation measures

1. The MAH shall agree the details of a controlled distribution system with the National Competent Authorities and must implement such programme nationally to ensure that:

- Prior to prescribing (and where appropriate, and in agreement with the national competent authority, prior to dispensing) all healthcare professionals who intend to prescribe (and dispense) Lenalidomide Mylan are provided with a physician information pack containing the following:
    - Educational health care professional's kit
    - Educational brochures for patients
    - Patient cards
    - Summary of product characteristics (SmPC) and package leaflet and labelling.

2. The MAH shall implement a pregnancy prevention programme (PPP) in each Member State. Details of the PPP should be agreed with the National Competent Authorities in each Member State and put in place prior to the launch of the product.
3. The MAH should agree on the implementation of the patient card system in each Member State.

Key elements to be included

The Educational Healthcare Professional's Kit

The Educational Health Care Professional's Kit shall contain the following elements:

- Brief background on lenalidomide and its licensed indication
- Posology
- Maximum duration of treatment prescribed
    - 4 weeks treatment for women with childbearing potential
    - 12 weeks treatment for men and women without childbearing potential
- The need to avoid foetal exposure due to teratogenicity of lenalidomide in animals and the expected teratogenic effect of lenalidomide in humans including a summary of the results of study CC-5013-TOX-004
- Guidance on handling the blister or capsule of Lenalidomide Mylan for healthcare professionals and caregivers
- Obligations of the health care professional in relation to the prescribing of Lenalidomide Mylan
    - 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 Mylan
    - Need to provide patients with appropriate patient educational brochure and patient card
- Safety advice relevant to all patients
    - Disposal of unwanted medicine
    - Local country specific arrangements for a prescription for Lenalidomide Mylan to be dispensed
    - Description of risk of tumour flare reaction
    - Description of risk of SPM
- Description of the PPP and categorisation of patients based on sex and childbearing potential
    - Algorithm for implementation of PPP
    - Definition of women of childbearing potential (WCBP) and actions the physician should take if unsure
- Safety advice for women of childbearing potential
    - The need to avoid foetal exposure
    - Description of the PPP
    - Need for adequate contraception (even if woman has amenorrhoea) and definition of adequate contraception
    - Pregnancy test regime
        - Advice on suitable tests
        - Before commencing treatment
        - During treatment based on method of contraception
        - After finishing treatment
    - Need to stop Lenalidomide Mylan immediately upon suspicion of pregnancy
    - Need to tell treating doctor immediately upon suspicion of pregnancy
- Safety advice for men
    - The need to avoid foetal exposure
    - The need to use condoms if sexual partner is pregnant or a WCBP not using effective contraception (even if man has had a vasectomy)

        - During Lenalidomide Mylan treatment
        - For at least 7 days following final dose.
    - That if his partner becomes pregnant whilst he is taking Lenalidomide Mylan or shortly after he has stopped taking Lenalidomide Mylan he should inform his treating doctor immediately
- Requirements in the event of pregnancy
    - Instructions to stop Lenalidomide Mylan immediately upon suspicion of pregnancy, if female patient
    - Need to refer to physician specialised or experienced in dealing with teratology and its diagnosis for evaluation and advice
    - Local contact details for reporting of any suspected pregnancy
    - Pregnancy reporting form
- Check list for physicians ensuring that patients receive the appropriate counselling concerning the treatment, contraceptive methods and pregnancy prevention appropriate for their sex and childbearing status at treatment initiation.
- Adverse event reporting forms

Educational Brochures for patients

The Educational brochures for patients should be of 3 types:

- Brochure for women patients of childbearing potential
- Brochure for women patients who are not of childbearing potential
- Brochure for male patients

All patient brochures should contain the following elements:

- That lenalidomide is teratogenic in animals and is expected to be teratogenic in humans
- Description of the patient card and its necessity
- Disposal of unwanted medicine
- Guidance on handling lenalidomide for patients, caregivers and family members
- National or other applicable specific arrangements for a prescription for Lenalidomide Mylan to be dispensed
- That the patient should not give Lenalidomide Mylan to any other person
- That the patient should not donate blood during therapy (including during dose interruptions) and for at least 7 days after discontinuation of Lenalidomide Mylan treatment
- That the patient should tell their doctor about any adverse events

The following information should also be provided in the appropriate brochure:

Brochure for women patients with childbearing potential

- The need to avoid foetal exposure
- Description of the PPP
- Need for adequate contraception and definition of adequate contraception
- Pregnancy test regime
    - Before commencing treatment
    - During treatment, at least every 4 weeks except in case of confirmed tubal sterilisation
    - After finishing treatment
- The need to stop Lenalidomide Mylan immediately upon suspicion of pregnancy

- The need to contact their doctor immediately upon suspicion of pregnancy

Brochure for male patients

- The need to avoid foetal exposure
- The need to use condoms if sexual partner is pregnant or a WCBP not using effective contraception (even if man has had vasectomy)
    - During Lenalidomide Mylan treatment
    - For at least 7 days following final dose
- That if his partner becomes pregnant, he should inform his treating doctor immediately
- That he should not donate semen or sperm during therapy (including during dose interruptions) and at least for 7 days after discontinuation of Lenalidomide Mylan treatment

Patient Card

The patient card shall contain the following elements:

- Verification that appropriate counselling has taken place
- Documentation of childbearing status potential
- Pregnancy test dates and results

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

The Member States should ensure that all conditions or restrictions with 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 Mylan 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:

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- Safety advice for men
    - The need to avoid foetal exposure
    - The need to use condoms if sexual partner is pregnant or a WCBP not using effective contraception (even if man has had a vasectomy)
        - During Lenalidomide Mylan treatment

        - For at least 7 days following final dose.
    - That if his partner becomes pregnant whilst he is taking Lenalidomide Mylan or shortly after he has stopped taking Lenalidomide Mylan he should inform his treating doctor immediately
- Requirements in the event of pregnancy
    - Instructions to stop Lenalidomide Mylan immediately upon suspicion of pregnancy, if female patient
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- That the patient should not give Lenalidomide Mylan to any other person
- That the patient should not donate blood during therapy (including during dose interruptions) and for at least 7 days after discontinuation of Lenalidomide Mylan treatment
- That the patient should tell their doctor about any adverse events

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    - After finishing treatment
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- The need to contact their doctor immediately upon suspicion of pregnancy

Brochure for male patients

- The need to avoid foetal exposure
- The need to use condoms if sexual partner is pregnant or a WCBP not using effective contraception (even if man has had vasectomy)
    - During Lenalidomide Mylan treatment
    - For at least 7 days following final dose
- That if his partner becomes pregnant, he should inform his treating doctor immediately
- That he should not donate semen or sperm during therapy (including during dose interruptions) and at least for 7 days after discontinuation of Lenalidomide Mylan treatment

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