30 May 2024
EMA/290725/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Pomalidomide Zentiva

International non-proprietary name: Pomalidomide

Procedure No. EMEA/H/C/006294/0000

Note

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

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Table of contents

List of abbreviations

ADR	adverse drug reactions
AE	adverse events
ASMF	active substance master file = drug master file
AE	adverse event
ANOVA	analysis of variance
AR	assessment report
AAS	atomic absorption spectrometry
BE	bioequivalence
BMI	body mass index
CoA	certificate of analysis
CEP	certificate of suitability of the EP
CFU	colony forming units
CI	confidence interval
DP	decentralised (application) procedure
DSC	differential scanning calorimetry
DPM	drug product manufacturer
ECG	electrocardiogram
ERA	environmental risk assessment
EC	European Committee
EP	European Pharmacopoeia
λ_z	first order rate constant associated with the terminal portion of the curve
GCP	good clinical practice
GLP	good laboratory practice
LC/MS/MS	liquid chromatography coupled with tandem mass spectrometry
C_{max}	maximum plasma concentration
PK	pharmacokinetic
RSD	relative standard deviation
rpm	rotation per minute
SD	standard deviation
SmPC	summary of product characteristics
AUC	area under the plasma concentration
$AUC_{0-\infty}$	area under the plasma concentration - time curve from time 0 to infinity
AUC_{0-t}	area under the plasma concentration - time curve from time 0 to t hours
CV%	coefficient of variation
CHMP	the Committee for Medicinal Products for Human Use
$t_{1/2}$	elimination or terminal half-life
T_{max}	time of the maximum measured plasma concentration

Not all abbreviations may be used.

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Zentiva, k.s. submitted on 9 August 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Pomalidomide Zentiva, 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 23 February 2023.

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 in the Union on the basis of a complete dossier in accordance with Article 8(3).

The applicant applied for the following indications:

Pomalidomide Zentiva in combination with bortezomib and dexamethasone is indicated in the treatment of adult patients with multiple myeloma who have received at least one prior treatment regimen including lenalidomide.

Pomalidomide Zentiva in combination with dexamethasone is indicated in the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy.

1.2. Legal basis, dossier content

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 Imnovid 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: Imnovid, 1mg, 2mg, 3mg, 4mg, capsules hard
- Marketing authorisation holder: Bristol-Myers Squibb Pharma EEIG
- Date of authorisation: 05-08-2013
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number:
- 1mg - EU/1/13/850/001; 005
- 2mg - EU/1/13/850/002; 006
- 3mg - EU/1/13/850/003; 007
- 4mg - EU/1/13/850/004; 008

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

reference medicinal product:

- Product name, strength, pharmaceutical form: Imnovid, 1mg, 2mg, 3mg, 4mg, capsules hard
- Marketing authorisation holder: Bristol-Myers Squibb Pharma EEIG
- Date of authorisation: 05-08-2013
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number:
- 1mg - EU/1/13/850/001; 005
- 2mg - EU/1/13/850/002; 006
- 3mg - EU/1/13/850/003; 007
- 4mg - EU/1/13/850/004; 008

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: Imnovid 4mg, capsules hard
- Marketing authorisation holder: Bristol-Myers Squibb Pharma EEIG
- Date of authorisation: 05-08-2013
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number(s): EU/1/13/850/004 and 008
- Bioavailability study number: CT.PLM.cap4.19.001(SHO-P4-644)

1.3. Information relating to orphan market exclusivity

1.3.1. 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.

1.4. Scientific advice

The applicant did not seek scientific advice from the CHMP.

1.5. Steps taken for the assessment of the product

The Rapporteur was appointed by the CHMP and by the PRAC.

The application was received by the EMA on	9 August 2023
The procedure started on	28 September 2023

The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	18 December 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	3 January 2024
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	25 January 2024
The applicant submitted the responses to the CHMP consolidated List of Questions on	22 February 2024
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	3 April 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 April 2024
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	25 April 2024
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	1 May 2024
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	15 May 2024
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 Pomalidomide Zentiva on	30 May 2024
The CHMP adopted a report on similarity of Pomalidomide Zentiva with Kyprolis (carfilzomib), Imnovid (pomalidomide), Ninlaro (ixazomib), Farydak (panobinostat), Darzalex (daratumumab), Blenrep (belantamab mafodotin), Abecma (idecabtagene vicleucel), Carvykti (Ciltacabtagene autoleucel) and Talvey(talquetamab)	30 May 2024

2. Scientific discussion

2.1. Introduction

This application concerns a generic application of a centrally authorised medicinal product according to Article 10(1) of Directive 2001/83/EC as amended.

The applicant has developed Pomalidomide Zentiva capsule, hard as generic to the reference product Imnovid 1 mg, 2 mg, 3 mg, 4 mg hard capsule.

The indication, posology and pharmacology as presented in the proposed SmPC are shown below.

Therapeutic indication

Pomalidomide Zentiva in combination with bortezomib and dexamethasone is indicated in the treatment of adult patients with multiple myeloma who have received at least one prior treatment regimen including lenalidomide.

Pomalidomide Zentiva in combination with dexamethasone is indicated in the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy.

Posology and method of administration

The posology and method of administration are in line with the reference product.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as hard capsules containing 1 mg, 2 mg, 3 mg, 4 mg of pomalidomide as active substance.

Other ingredients are:

Capsule contents: microcrystalline cellulose, maltodextrin, and sodium stearyl fumarate.

Capsule shell: gelatin, titanium dioxide (E171), iron oxide yellow (E172), iron oxide red (E172), indigo carmine aluminium lake (E132) (3 mg and 4 mg strength only), and erythrosine (E127) (4 mg strength only)

Printing ink (white ink): shellac, titanium dioxide (E171), and propylene glycol (E1520)

The product is available in OPA/Al/PVC/Al blister packs as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of active substance is 4-amino-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione corresponding to the molecular formula $C_{13}H_{11}N_3O_4$. It has a relative molecular mass of 273.24 g/mol and the following structure:

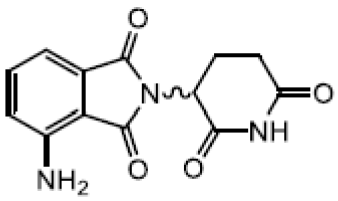


Figure 1: Active substance structure

The chemical structure of the active substance was elucidated by a combination of elemental analysis, IR spectroscopy, ^{1}H-NMR, ^{13}C-NMR, and mass spectrometry (MS).

The active substance is a non-hygroscopic yellow powder, slightly soluble in acetone, acetonitrile, methylene chloride, methyl ethyl ketone, and tetrahydrofuran. Pomalidomide is very slightly soluble in ethanol, ethyl acetate, methanol, 2- propanol, and toluene and practically insoluble in water and aqueous media across the physiological pH range.

Pomalidomide is a chiral compound with one asymmetric carbon centre. The active substance is marketed as the racaemic mixture

Polymorphism has not been observed in the active substance.

Manufacture, characterisation and process controls

The active substance is manufactured by one manufacturing site.

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

The active substance is synthesised in 2 main steps using well defined starting materials with acceptable specifications. During evaluation a major objection (MO) was raised by the CHMP in the restricted part of the ASMF requesting the re-definition of the proposed starting materials. Additional justification for the proposed starting material was provided by the applicant and the response was considered satisfactory.

Potential and actual impurities were well discussed with regards to their origin and characterised.

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

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The primary contact material complies with EC 10/2011 as amended.

Specification

The active substance specification by the manufacturer of finished product includes tests for appearance (visual), identification (IR, HPLC), loss on drying (Ph. Eur.), sulphated ash (Ph. Eur.), residual solvents (GC), impurities (HPLC), assay (HPLC), optical rotation (Ph. Eur.), particle size distribution (Ph. Eur.), and microbial contamination (Ph. Eur.).

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 testing has been presented.

Batch analysis data (3 commercial scale batches) of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 3 commercial scale batches of active substance from the manufacturer stored in in a container closure system representative of that intended for the market 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: appearance, identification, loss on drying, impurities and assay. No significant changes to any of the measured parameters were observed under long term and accelerated conditions.

Photostability testing following the ICH guideline Q1B was performed on 1 batch. No changes in physical properties (e.g., appearance, identification and loss on drying) or chemical characteristics (e.g. assay and impurities) were observed. All results remained within the specification limits. Pomalidomide is therefore considered to be photostable.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable.

2.2.3. Finished medicinal product

Description of the product and pharmaceutical development

The finished product is presented as follows:

1 mg strength: hard gelatin capsule, with a yellow body and red cap, with "PLM 1" printed in white ink on the capsule body. Capsule size 4 (approximately 14.3 mm in length).

2 mg strength: hard gelatin capsule, with an orange body and red cap, with "PLM 2" printed in white ink on the capsule body. Capsule size 2 (approximately 18 mm in length).

3 mg strength: hard gelatin capsule, with a turquoise body and red cap, with "PLM 3" printed in white ink on the capsule body. Capsule size 2 (approximately 18 mm in length).

4 mg strength: Hard gelatin capsule, with a dark blue body and red cap, with "PLM 4" printed in white ink on the capsule body. Capsule size 2 (approximately 18 mm in length).

The finished product has been developed to be a generic equivalent to the reference medicinal product Imnovid. Consequently, the objective was to prepare a hard capsule being essentially similar to the reference medicinal product.

As the active substance exhibits very low solubility in aqueous media across the physiological pH range.

No incompatibilities between the active substance and the excipients have been found in literature, nor have been observed during the stability studies.

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

The objective of the formulation development was to develop hard gelatin capsules containing 1, 2, 3 and 4 mg of pomalidomide with a dissolution and stability profile comparable to reference medicinal product. Quality by design was applied to develop the generic medicinal product; however, no design space was claimed for the finished product.

Based on the clinical and pharmacokinetic (PK) characteristics as well as the *in vitro* dissolution, a quality target product profile (QTPP) was defined for the finished product

A list of quality attributes (QA) was identified and it was discussed why some were identified as critical.

During formulation optimisation, different types of fillers, addition of a disintegrant and stability of the proposed formulation were investigated.

A dissolution method was established for the finished product. The effect of different paddle speed was evaluated.

The dissolution method was found to be discriminatory (for the proposed dissolution limit) with respect to i particle size and stressed capsules

In vivo bioequivalence has been evaluated and demonstrated between the 4 mg capsules of the test formulation and the reference product. To support the results obtained in the bioequivalence study, the test of one batch of the bio-batch of the proposed 4 mg product and the reference medicinal product Imnovid 4 mg were tested.

The *in vitro* dissolution of test and reference products can be considered similar the in *vivo* results show they are equivalent.

Comparative dissolution profiles were provided for one batch of the 1 mg, 2 mg and 3 mg strengths versus the 4 mg biobatch. Dissolution was observed across the physiological pH range, the f2-values were calculated for each strength in all three media.

Biowaiver of strengths 1 mg, 2 mg and 3 mg was applied. However, the biowaiver of lower strengths could not be accepted during the evaluation (MO), as not all conditions for the biowaiver were met. The comparative dissolution tests in support of the requested biowaiver of strengths were conducted.

On the basis of the MO, comparative *in vitro* dissolution testing was performed with the 1 mg, 2 mg and 3 mg strength and the biobatch of 4 mg strength in three pH media (pH 1.0, pH 4.5 and pH 6.8). As variability was too high, similarity factors were calculated using the bootstrapping method. I

The applicant provided further information, based on that the biowaiver claim for the lower strengths (1 mg, 2 mg and 3 mg) at 100 rpm is considered acceptable as the coning effect is observed at lower speed (50 rpm). The applicant has sufficiently justified that the 5 min timepoint can be ignored as it is not considered clinically relevant, given the capsule formulation. In this specific case, there are still sufficient time points to allow comparison of dissolution profiles without the 5-minute timepoint.

The manufacturing process development studies were based on the initial risk assessment. Previous experience was used to determine the degree of risk associated with each process step and its impact on the CQAs of the finished product.

Based on the results of the development studies, the control strategy for pomalidomide lab scale batches was determined, which includes pomalidomide and excipient material attributes to be controlled, proposed in-process controls and proposed ranges for the high-risk process parameters based on the development results.

Upon manufacturing the scale up trial and qualification batches, it can be concluded that all the manufacturing steps for pomalidomide capsules (e.g., sieving of materials, blending and encapsulation) are reproducible and suitable for manufacturing the validation batches.

The primary packaging is OPA/Al/PVC/Al blister packs. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The finished product is manufactured by one manufacturing site.

The manufacturing process consists of 5 main steps: blend preparation, lubrication, encapsulation and packaging. The manufacturing process is considered to be non-standard, as the content of the active substance is low.

Major steps of the manufacturing process have been validated by a number of studies on three consecutive commercial scale batches. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form: appearance (visual), water content (KF), dissolution (Ph. Eur.), uniformity of dosage units (Ph. Eur.), identification (HPLC, UV), assay (HPLC), impurities (HPLC), and microbial contamination (Ph. Eur.).

The proposed specification for the finished product is in line with ICH Q6A and it is generally acceptable for this type of dosage form.

The limit for the largest unspecified impurity is in line with ICH Q3B and is acceptable. The shelf-life limit for total impurities is in line with stability data and is acceptable.

Dissolution testing with a limit of Q=80 % in 45 minutes was initially set. This limit was not in accordance with the Reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action EMA/CHMP/CVMP/QWP/336031/2017. Therefore, tightening of the dissolution limit was requested as an MO by the CHMP. The dissolution limit was tightened to ≥ 75% (Q) in 30 minutes for all strengths which was accepted.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach. The evaluation of daily contribution of each individual component (i.e., active substance and excipients) has been provided for worst-case approach. None of the elemental impurities exceeded 30% PDE threshold as per ICH Q3D so it was concluded that no further control of potential elemental impurities is needful at release or during the manufacturing process. It is acceptable that no additional controls are adopted.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and

answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

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 testing has been presented.

Batch analysis results were provided for 3 commercial scale batches per strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from 3 commercial batches per strength of finished product stored for up to 36 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 the medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, water content, dissolution, assay, and microbial contamination. The analytical procedures used are stability indicating. All stability results under long term and accelerated conditions were within the proposed specification limits. There is an increase in water content, however the other product quality parameters are not affected.

A bulk stability study was performed in one batch per strength at 25°C / 60% RH. No significant changes were observed compared with the initial data.

In addition, one batch per strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No trends or out-of-specification results were observed. The results indicate that the finished product is photostable.

Based on available stability data, the proposed shelf-life of 3 years without special storage conditions as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

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

During evaluation, 3 major objections were raised by the CHMP in relation to definition of starting materials, dissolution data in support of the biowaiver of strengths and QC dissolution testing limits. The responses from the applicant to the MOs were considered satisfactory and all the issues were

considered resolved, as explained above. 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.

The applicant has applied QbD principles in the development of the finished product and its manufacturing process. However, no design space was claimed for the manufacturing process of the the finished product.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered 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

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

2.3.3. Discussion on non-clinical aspects

The non-clinical sections of the proposed SmPC are identical to the reference product Imnovid.

The submitted non-clinical overview on the pre-clinical pharmacology, pharmacokinetics, and toxicology of pomalidomide is adequate. Grounds for non-providing new clinical data are adequately justified. The impurity profile and the safety of the excipients are considered acceptable.

Since proposed product is a generic product which does not include the addition of a new indication, a new patient population, or an increase in the maximum recommended therapeutic dose, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

2.3.4. Conclusion on the non-clinical aspects

There are no objections to approval of Pomalidomide Zentiva from a non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for hard capsules containing pomalidomide. To support the marketing authorisation application the applicant conducted one bioequivalence study with a cross-over design under fasting conditions. This study was the pivotal study for this application.

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) as well as the Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/09 are of particular relevance.

GCP aspect

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

A biowaiver was requested for 1 mg, 2 mg and 3 mg strengths based on the following arguments:

- The 1 mg, 2 mg, 3 mg and 4 mg strengths were manufactured by the same manufacturer via the same process.
- The pharmacokinetics of pomalidomide is linear across the clinical dose range.
- The qualitative composition of the tablet content of pomalidomide 1 mg, 2 mg, 3 mg and 4 mg capsules is the same.
- The ratio between the amounts of the active substance and the excipients in the pomalidomide 1 mg, 2 mg, 3 mg and 4 mg capsules is the same (i.e. they are quantitatively proportional).

The *in vitro* comparative dissolution profiles of the pomalidomide Zentiva capsules in physiologic pHs are summarised in **Table 1**.

Table 1. *In vitro* dissolution data for biowaiver request including test conditions and apparatus settings

Dissolution testing site		Synthon Hispania S.L., Calle De Castello 1, Sant Boi De Llobregat, Barcelona 08830, Spain
Dissolution condition	***Apparatus***	Ph.Eur. Apparatus II (paddle)
	Stirring speed	100 rpm
	Volume	900 ml
	Temperature	37 ± 0.5°C

Medium: pH 1.0 (HCl 0.1 N) n = 12	0 min	5 min	10 min	15 min	20 min	30 min	45 min	60 min	f_2
1 mg batch 190077	0	37.6	64.4	77.5	84.7	91.3	95.0	96.5	**60**
2 mg batch 190040	0	28.0	53.7	65.0	73.3	81.5	88.0	90.8	**67**
3 mg batch 190043	0	30.9	54.0	66.0	73.4	81.9	88.2	91.4	**71**
4 mg batch 190048	0	34.3	59.4	69.7	77.1	84.6	90.6	93.1	
Medium: pH 4.5 (acetate buffer) n = 12	0 min	5 min	10 min	15 min	20 min	30 min	45 min	60 min	f_2
1 mg batch 190077	0	29.0	58.7	72.6	80.8	88.9	93.6	95.5	**56**
2 mg batch 190040	0	19.8	48.3	61.8	70.8	80.6	87.9	91.5	**83**
3 mg batch 190043	0	23.7	50.5	62.1	70.8	79.8	87.2	90.7	**89**
4 mg batch 190048	0	25.1	51.6	64.0	72.2	81.1	87.8	91.3	
Medium: pH 6.8 (phosphate buffer) n = 12	0 min	5 min	10 min	15 min	20 min	30 min	45 min	60 min	f_2
1 mg batch 190077	0	35.7	65.2	77.2	84.4	90.7	94.1	95.2	**68**
2 mg batch 190040	0	23.8	54.3	67.9	75.6	83.5	88.9	91.9	**67**
3 mg batch 190043	0	32.4	56.6	68.9	75.8	83.0	88.2	90.7	**73**
4 mg batch 190048	0	33.8	60.3	72.1	79.3	87.0	92.0	94.2	

Note: In above table average values are presented. The individual values can be found in Module 3 – Section 2.P.2.2.1.

Tabular overview of clinical studies

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

Table 2. Tabular overview of clinical studies

Type of Study	*Study Identifier*	*Location of Study Report*	*Objective(s) of the Study*	*Study Design and Type of Control*	*Test Product(s); Dosage Regimen; Route of Administration*	*Number of Subjects*	*Healthy Subjects or Diagnosis of Patients*	*Duration of Treatment*	*Study Status; Type of Report*
BE	SHO-P4-644	Module 5 – Section 3.1.2	The objective of this study was to compare the bioavailability of Pomalidomide 4 mg capsules with Imnovid® 4 mg capsules (containing Pomalidomide) in healthy adult male volunteers under fasting conditions, and to assess the bioequivalence of these products.	Crossover, Fasting State	Two capsule formulations; 4 mg single dose; oral	38	Healthy Subjects	Single dose	Complete; Full

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

***Study* SHO-P4-644:** Single dose, open label, randomised, two-treatment, two-sequence, two-period, crossover bioequivalence study comparing Pomalidomide 4 mg capsules with Imnovid 4 mg capsules (containing pomalidomide) in healthy adult male subjects under fasting conditions.

Methods

- **Study design**

The study was a comparative, randomised, two-treatment, two-period, two-sequence, two-way crossover open label bioequivalence study on healthy volunteers with a single dose administration under fasting conditions. In each study period, subjects received a single oral dose of 4 mg

pomalidomide capsule (test) or a reference with 240 ml of water after an overnight fast (10 hrs). Fasting continued for at least 4 hours following drug administration, after which a standardised meal was served. Wash-out period was 7 days. Study periods:

Screening: within 28 days prior to the scheduled dosing day of Period I.

Dosing period I: 08.02.2020

Dosing period II: 15.02.2020

Analysis Dates: 21.02.2020 – 11.03.2020

- **Test and reference products**

Table 3. Overview of test and reference product

Product Characteristics	*Test Product*	*Reference Product*
Name:	Pomalidomide 4 mg capsules	Imnovid 4 mg hard capsules
Strength:	4 mg pomalidomide per capsule	4 mg pomalidomide per capsule
Dosage form:	Capsule	Capsule
Manufacturer:	Synthon Hispania S.L., Spain	Marketing Authorization Holder: Celgene Europe B.V., The Netherlands
Batch number:	190048	C2225AB
Batch size (biobatch):	11.0 kg (57,894 capsules)*	
Measured content(s): (% of label claim)	4.0 mg/capsule 100.9 %	4.1 mg/capsule 102.3 %
Commercial Batch Size:	11.0 kg (57,894 capsules)*	
Expiry date (Retest date):	December 2021	March 2022
Location of Certificate of Analysis:	Module 5.3.1.2 - Section 16.1.7.2	Module 5.3.1.2 - Section 16.1.7.2
Member State where the reference product is purchased from:		Denmark
This product was used in the following trials:	SHO-P4-644 (CT.PLM.cap4.19.001)	SHO-P4-644 (CT.PLM.cap4.19.001)

* Pomalidomide capsules is a generic of an orphan medicinal product (Imnovid) intended for the treatment of multiple myeloma. As volumes are expected to be low, a full commercial scale batch (less than 100,000 units) is used in the bioequivalence study.

The provided information was acceptable, the difference between actual contents of test and reference products was less than 5%. The reference product is EU registered.

Certificates of analysis of test and reference product were included in the dossier.

- **Population studied**

The inclusion criteria were: healthy subjects, male, aged 18-60 years, BMI within 18.5-30 kg/m^2 (both inclusive), non-smoker, not having any significant diseases or clinically significant abnormal findings during screening, medical history, clinical examination, laboratory evaluations, 12-lead ECG, having clinically acceptable laboratory value for liver function test and renal function test, no known allergy to the investigated product, able to understand and comply with the study procedures and having given their written informed consent were checked in for the study.

The exclusion criteria were:

- Used any prescription drugs in the 28 days prior to the first study drug administration, that in the opinion of an investigator would put into question the status of the participant as healthy.
- Positive test result for alcohol, cotinine and/or drugs of abuse at screening or prior to the first drug administration.
- Positive screening results to HIV Ag/Ab Combo, HBsAG or HCV tests.
- Intake of pomalidomide in the 28 days prior to the first study drug administration.
- Maintenance therapy with any drug or significant history of drug dependency or alcohol abuse (> 3 units of alcohol per day, intake of excessive alcohol, acute or chronic).

A total of 38 subjects were dosed and 37 completed the study. Data from these 37 subjects were used for pharmacokinetic and statistical analysis. Case report forms have been submitted.

One subject withdrew consent from the study for personal reasons after dosing of period 1 and only received the reference in period 1. Hence, the subject was excluded from the pharmacokinetic analysis. The handling of the drop-out was considered acceptable.

Protocol deviations

No major protocol deviations were reported.

- **Analytical methods**

A bioanalytical report concerning HPLC/MS/MS method for the determination of pomalidomide in human plasma was submitted. The method used was validated, and the validation report (PMD-V5-654(R2) was included in the dossier.

Total number of analysed samples was 1,574. The total number of analysed analytical runs is 10, no run had to be repeated.

Internal standard was Pomalidomide-15N-13C5, certificate of analysis is submitted. A set of 10 non-zero standards with calibration range (0.5 to 150 ng/mL) and 6 quality controls (1.5 to 112.5 ng/mL) were prepared on 19/02/20 and stored at a nominal temperature of -80°C.

A total number of 134 incurred samples were re-analysed, corresponding to 9% of 1,574 study samples and 96.3% of them met the acceptance criteria.

Stability of analyte in the plasma samples has been demonstrated. There were no measured sample concentrations above the calibrated upper limit of quantification. Analysis was performed in the blinded manner. The submitted validation report meets the criteria set by the guideline ICH M10 on bioanalytical method validation (EMA/CHMP/ICH/172948/2019). Handling of samples was adequate. There were no protocol and SOP deviations during the subject sample analysis.

- **Pharmacokinetic variables**

The following pharmacokinetic parameters were calculated for pomalidomide using standard non-compartmental methods:

Primary:

C_{max}: maximum measured plasma concentration over the time span specified.

AUC0-t: the area under the plasma concentration versus time curve, from time (0) to the last measurable concentration (t), as calculated by the linear trapezoidal method.

Secondary:

$AUC_{0-\infty:}$ the area under the plasma concentration versus time curve from time (0) to infinity.

T_{max}: time of the maximum measured plasma concentration.

$t_{1/2}$: the elimination or terminal half-life.

λ_Z: apparent elimination rate constant, estimated by linear regression of the terminal linear portion of the log concentration versus time curve

Residual area extrapolated area: (i.e. percentage of AUC0-∞ due to extrapolation from time of last observed quantifiable plasma concentration to infinity)

Pharmacokinetic variables were adequate.

- **Statistical methods**

The statistical evaluation of bioequivalence included the following: analysis of variance (ANOVA) in all derived pharmacokinetic parameters, calculation of formulations ratios (point estimates) and parametric 90% confidence interval for ln-transformed AUC0-t and Cmax parameters.

The influence of sequence, subject (sequence), treatment and period effect was tested as fixed factors.

Descriptive statistics: all pharmacokinetic parameters: arithmetic mean, SD, CV%, median, min and max.

90% Confidence intervals: logarithmically transformed test/reference ratios had to be within 80.00-125.00% for C_{max} and AUC_{0-t}.

Handling of missing values was appropriate. There were no outliers reported.

Statistical methods were acceptable according to the bioequivalence guideline (CPMP/EWP/QWP/1401/98 Rev. 1).

Criteria for conclusion of bioequivalence: The ratio of geometric LSmeans with corresponding 90% confidence interval calculated from the exponential of the difference between the Test and the Reference for the ln-transformed parameters C_{max} and AUC_{0-t} should be within the 80.00 to 125.00% bioequivalence acceptance range.

Results

Table 4. Summary of plasma pomalidomide pharmacokinetic arameters

PARAMETER	TEST (n=37)[b]		REFERENCE (n=37)[b]	
	MEAN	CV (%)	MEAN	CV (%)
C_{max} (ng/mL)	53.402	(20.7)	59.400	(21.1)
T_{max} (hours)[a]	3.00	(1.50-6.02)	2.00	(0.67-5.50)
AUC_{0-t} (ng·h/mL)	506.201	(30.2)	508.810	(31.7)
$AUC_{0-\infty}$ (ng·h/mL)	517.348	(30.1)	523.527	(30.6)
Residual area (%)	1.56	(46.7)	1.74	(54.0)
λ_Z ($hours^{-1}$)	0.1153	(19.7)	0.1161	(20.5)
t_{half} (hours)	6.23	(18.8)	6.21	(19.8)

[a] Median and range are presented

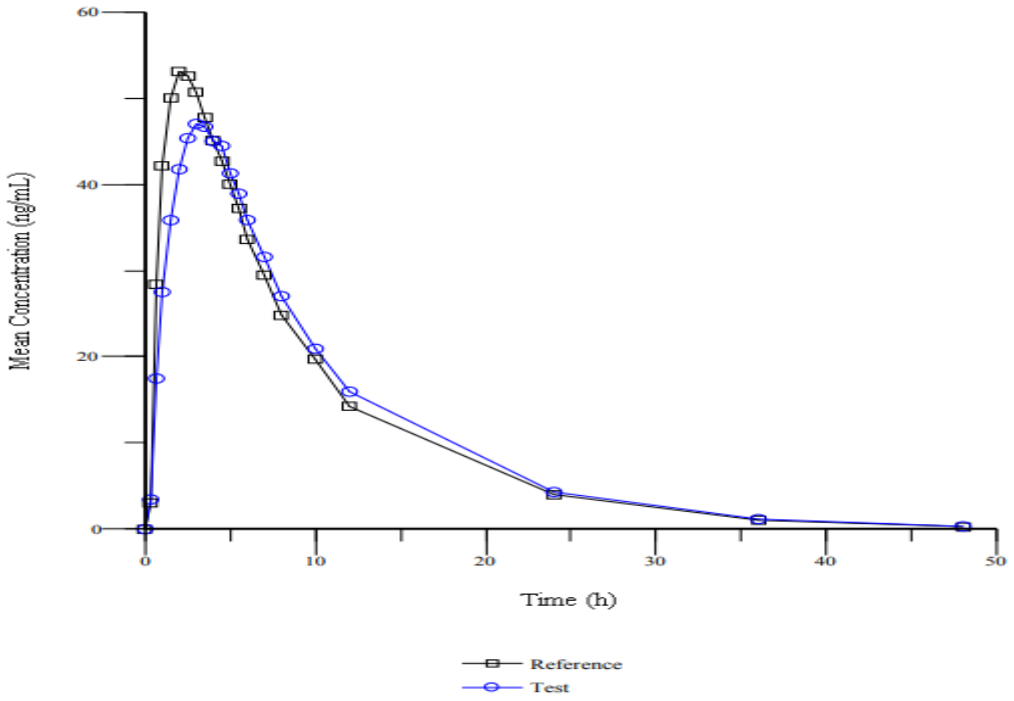
[b] n=36 for $AUC_{0-\infty}$, residual area, λ_Z, and t_{half}

Table 5. 90% confidence interval for ln-transformed AUC_{0-t} and C_{max} parameters

PARAMETER	INTRA-SUBJECT CV (%)	GEOMETRIC LSMEANS[a]		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		TEST (n=37)	REFERENCE (n=37)		LOWER	UPPER
C_{max}	10.8	52.356	58.215	89.94	86.23	93.81
AUC_{0-t}	7.1	486.056	486.929	99.82	97.07	102.65

[a] units are ng/mL for C_{max} and ng·h/mL for AUC_{0-t}

Figure 2. Mean pomalidomide concentration-time profiles after single-dose administration – PK population (linear scale)



No statistically significant sequence or period effects were observed for the ln-transformed Cmax data. No statistically significant treatment, sequence or period effects were observed for the ln-transformed AUC0-t data. A significant treatment effect was observed for ln-transformed Cmax. Since bioequivalence assessment is based on a CI approach that tests the similitude of the 2 products rather than on a p-value approach that tests differences between the 2 products, significant statistical differences between treatments do not have an impact on the bioequivalence assessment between the 2 formulations.

Mean residual area values were 1.56% and 1.74% for the Test and Reference formulations, respectively. All subjects had plasma concentration curves where the residual area was < 20%. It is thus considered that the sampling schedule covered the plasma concentration time curve long enough to provide a reliable estimate of the extent of exposure.

There were no pre-dose concentrations of pomalidomide greater than 5% of Cmax. Cmax was not observed in any case at the first time point after dosing.

- ***Safety data***

No serious AEs and no deaths were reported for any of the subjects dosed in this study. No subject was withdrawn by the investigator due to an AE (safety reasons).

A total of 18 AEs were experienced by 9 of the 38 subjects (24%) who participated in this study. Of these AEs, 10 occurred after administration of the test product and 8 occurred after administration of the reference product. Most of the AEs experienced during the study were considered drug-related (17/18; 94%). All AEs experienced during the study were resolved or were resolving at the end of the study.

The AE experienced most commonly in this study was headache, reported by 1 subject (3%) after administration of the test product and 3 subjects (8%) after administration of the reference product.

Another AE experienced less frequently included fatigue, reported by 2 subjects (5%) after administration of the test. The remaining AEs of dizziness, hypoaesthesia, vessel puncture site swelling, abdominal pain upper, dry mouth, increased appetite, muscular weakness, cough, erythema, and pruritus were experienced by no more than 1 subject (3%) per treatment group.

The incidence of AEs was similar for subjects dosed with the test product and the reference product (14% and 16%, respectively). Drug-related AEs were reported with similar incidence for subjects dosed with the test product and the reference product (11% and 16%, respectively). The AEs experienced during the study were deemed mild (17/18, 94%) and moderate (1/18, 6%) in severity. None of the subjects experienced a severe AE during the study.

In general, there were no clinical laboratory results that were considered clinically significant by the investigator. Furthermore, there were no out-of-range vital signs considered clinically significant reported in this study.

2.4.2.2. Pharmacodynamics

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

2.4.3. Discussion on clinical aspects

Pomalidomide Zentiva 4 mg hard capsules was compared with Imnovid 4 mg hard capsules in a bioequivalence study in healthy adult volunteers under fasting conditions. The design of the submitted study was acceptable. As the medicinal product can be used with or without food, the dosing in the fasting state was preferable.

For the lower strengths, 1 mg, 2 mg and 3 mg, a biowaiver was requested. The comparative dissolution tests in support of the requested biowaiver of strengths were conducted. at 100 rpm.

The applicant demonstrated that the coning effect occurred at 50 rpm. Therefore, the selected higher paddle speed of 100 rpm was justified. In addition, comparing dissolution profiles omitting the 5-minute time point was also considered acceptable, considering the high variability which was observed and that such an early time point is not clinically relevant and is also in accordance with Guideline on the investigation of bioequivalence. The request of the biowaiver of lower strengths was thus considered acceptable.

The wash-out period is long enough regarding the median plasma half-life of 9.5 hours in healthy volunteers (according to the SmPC of the reference product). The sampling period was sufficient to characterise the plasma concentration-time profile considering that C_{max} is achieved between the first 2 and 3 hours after administration.

The study population and the sample s were acceptable. The exclusion and inclusion criteria were acceptable. There was no exclusion criterium with regards to race and only male subjects were enrolled. This is appropriate as no race or gender effect on PK is reported.

Bioequivalence between the two formulations of pomalidomide has been demonstrated. 90% CIs fall into the predefined limit 80-125%, for both AUC0-t and C_{max}. As no C_{max} was measured in any of the samples at the first time point, the sampling scheme has been chosen correctly.

The significant fixed effect for treatment for C_{max} was justified. It is agreed that in case of generics, it is crucial that the test product stays within the accepted confidence interval with regards to the reference product while crossing the unity is not necessary.

The impact of missing data for one subject for $AUC_{0-\infty}$ is considered as negligible because the extent of extrapolated AUC area was generally very small, with the maximum at 5%.

2.4.4. Conclusions on clinical aspects

Based on the presented bioequivalence study, Pomalidomide Zentiva is considered bioequivalent with Imnovid.

The results of study SHO-P4-644 with the 4mg formulation can be extrapolated to other strengths 1mg, 2mg, 3mg, according to conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1, section 4.1.6.

2.5. Risk Management Plan

2.5.1. Safety concerns

Table 6. Summary of safety concerns

Important identified risks	• Teratogenicity • Severe infection due to neutropenia and pancytopenia • Thrombocytopenia and bleeding • Cardiac failure • Non-melanoma skin cancer
Important potential risks	• Other second primary malignancies • Cardiac arrhythmia
Missing information	• None

2.5.2. Pharmacovigilance plan

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 3 - Required additional pharmacovigilance activities				
Monitoring of PPP implementation Planned	To monitor the implementation of the PPP on a country-specific basis.	Teratogenicity	Data will be collected on a regular basis after product launch and results will be reported in PSURs in accordance with the PSUR schedule.	In accordance with the PSUR schedule.

2.5.3. Risk minimisation measures

Safety concern	**Risk minimisation measures**
Teratogenicity	<u>Routine risk minimisation measures:</u> SmPC

Safety concern	Risk minimisation measures
	Contraindicated in pregnant women and in women of childbearing potential, unless all the conditions of the PPP are met. Pomalidomide is also contraindicated in male patients unable to follow or comply with the required contraceptive measures (Section 4.3). Warnings: criteria for women of non-childbearing potential, counselling, contraception, pregnancy testing, precautions for men, additional precautions, prescription duration (Section 4.4). Stringent controls are required to ensure exposure of an unborn child to pomalidomide does not occur (Section 4.4). These include: counselling, contraception, pregnancy testing, precautions for men, additional precautions and prescription duration. PL The PL warns of the potential teratogenic effects of pomalidomide and the need to avoid pregnancy. Additional risk minimisation measures: Zentiva PPP Educational Programme Educational HCP's kit to include educational healthcare professional brochure, educational brochures for patients, patient card, risk awareness forms, and information on where to find latest SmPC. Therapy management Criteria for determining women of childbearing potential, contraceptive measures and pregnancy testing for women of childbearing potential. Advice in SmPC and educational materials. System to ensure appropriate measures have been completed Patient Card to document childbearing status, counselling and pregnancy testing.
Severe infection due to neutropenia and pancytopenia	<u>Routine risk minimisation measures:</u> SmPC Dose modification advice for neutropenia (Section 4.2). Warning of neutropenia, and advice for blood tests at baseline, weekly for the first 8 weeks and monthly thereafter (Section 4.4). Warning regarding HBV reactivation and advice that HBV status should be established before treatment (Section 4.4). Neutropenia, pancytopenia and infections and infestations are listed as ADRs and neutropenia and infection are discussed in Section 4.8. PL Advice to patients including a warning that the doctor is advised to check if the patient has ever had hepatitis B infection prior to starting pomalidomide treatment. A warning that pomalidomide may cause a fall in the number of RBCs, WBCs, and platelets at the same time (pancytopenia), and describes possible symptoms. <u>Additional risk minimisation measures:</u> None
Thrombocytopenia and bleeding	<u>Routine risk minimisation measures:</u> SmPC Dose modification advice for thrombocytopenia (Section 4.2).

Safety concern	Risk minimisation measures
	Warning of thrombocytopenia, and advice for blood tests at baseline, weekly for the first 8 weeks and monthly thereafter. Advice to monitor for signs of bleeding (Section 4.4) Thrombocytopenia, intracranial haemorrhage and gastrointestinal haemorrhage are listed as ADRs and discussed in Section 4.8. PL The PL warns that pomalidomide may cause bleeding or bruising without a cause, and lists bleeding within the skull, nosebleeds and bleeding from the bowels or stomach as possible side effects. <u>Additional risk minimisation measures:</u> Educational HCP brochure. Educational brochure for patients.
Cardiac failure	<u>Routine risk minimisation measures:</u> SmPC Section 4.4 of the SmPC provides warnings and precautions regarding treating patients with cardiac risk factors, and advice regarding periodic monitoring for signs or symptoms of cardiac events. Listed as an ADR in Section 4.8. PL A warning regarding heart failure is included in the PL. <u>Additional risk minimisation measures:</u> Educational HCP brochure.
Non-melanoma skin cancer	<u>Routine risk minimisation measures:</u> SmPC Section 4.4 contains a warning that SPM, such as NMSC, have been reported in patients receiving pomalidomide; physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of SPM and institute treatment as indicated. BCC of the skin and SCC of the skin are listed as ADRs in Section 4.8. PL A warning regarding BCC and SCC is included in the PL. <u>Additional risk minimisation measures:</u> None
Other second primary malignancies	<u>Routine risk minimisation measures:</u> SmPC Section 4.4 states that SPM have been reported in patients receiving pomalidomide, and warns that physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of SPM and institute treatment as indicated. Preclinical safety data discussed in Section 5.3. PL A warning regarding BCC and SCC is included in the PL. <u>Additional risk minimisation measures:</u> None

Safety concern	Risk minimisation measures
Cardiac arrhythmia	Routine risk minimisation measures: SmPC AF listed as an ADR in Section 4.8. PL AF listed in PL. Additional risk minimisation measures: None

2.5.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 1.0is acceptable.

2.6. Pharmacovigilance

2.6.1. 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.

2.6.2. 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 Imnovid 1 mg, 2 mg, 3 mg and 4 mg hard capsules and Ibuprofen Zentiva 400 mg, 600 mg and 800 mg film-coated tablets. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

This application concerns a generic version of pomalidomide, capsules, hard. The reference product Imnovid is indicated in combination with bortezomib in the treatment of adult patients with multiple myeloma who have received at least one prior treatment regimen including lenalidomide and in combination with dexamethasone is indicated in the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy.

No non-clinical studies have been provided for this application but an adequate summary of the available non-clinical 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 is considered sufficient.

The bioequivalence study forms the pivotal basis with the following design: comparative, randomised, balanced, two-treatment, two-period, two-sequence, two-way crossover open label bioequivalence study on healthy volunteers with a single dose administration under fasting conditions. The study design is 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 are adequate.

The test formulation of Pomalidomide Zentiva 4 mg met the protocol-defined criteria for bioequivalence when compared with the Imnovid 4 mg. The point estimates and their 90% confidence intervals for the parameters AUC_{0-t} and C_{max} were all contained within the protocol-defined acceptance range of 80.00 to 125.00%. Bioequivalence of the two formulations was demonstrated.

For the lower strengths, the applicant submitted no bioequivalence studies and requested a biowaiver which was accepted.

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

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Pomalidomide Zentiva is not similar to Abecma (Idecabtagene vicleucel), Blenrep (Belantamab mafodotin), Carvykti (Ciltacabtagene autoleucel), Darzalex (Daratumumab), Farydak (Panobinostat), Kyprolis (Carfilzomib), Ninlaro (Ixazomib), and Talvey (talquetamab) within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000.

Outcome

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

Pomalidomide Zentiva in combination with bortezomib and dexamethasone is indicated in the treatment of adult patients with multiple myeloma who have received at least one prior treatment regimen including lenalidomide.

Pomalidomide Zentiva in combination with dexamethasone is indicated in the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy.

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

conditions:

Conditions or restrictions regarding supply and use

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

Other conditions and requirements of the marketing authorisation

- ***Periodic Safety Update Reports***

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

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

- **Risk Management Plan (RMP)**

The marketing authorisation holder (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 access programme with the National Competent Authorities and must implement such programme nationally to ensure that:

- Prior to prescribing (where appropriate, and in agreement with the National Competent Authority, dispensing) all healthcare professionals who intend to prescribe (and dispense) Pomalidomide Zentiva are provided with an Educational Healthcare Professional's Kit containing the following:
  - Educational Healthcare Professional brochure
  - Educational brochures for patients
  - Patient card Risk awareness forms
  - Information on where to find latest Summary of Product Characteristics (SmPC)

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 medicinal product.
3. The MAH should agree the contents of the Educational Healthcare Professional's Kit with the National Competent Authority in each Member State prior to launch of the medicinal product and ensure that the materials contain the key elements as described below.
4. The MAH should agree on the implementation of the controlled access programme in each Member State.

<u>Key elements to be included</u>

Educational Healthcare Professional's Kit

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

Educational Healthcare Professional brochure

- Brief background on pomalidomide
- Maximum duration of treatment prescribed
    - 4 weeks for women with childbearing potential
    - 12 weeks for men and women without childbearing potential
- The need to avoid foetal exposure due to teratogenicity of pomalidomide in animals and the expected teratogenic effect of pomalidomide in humans
- Guidance on handling the blister or capsule of Pomalidomide Zentiva for healthcare professionals and caregivers
- Obligations of the healthcare professionals who intend to prescribe or dispense Pomalidomide Zentiva
    - Need to provide comprehensive advice and counselling to patients
    - That patients should be capable of complying with the requirements for the safe use of Pomalidomide Zentiva
    - Need to provide patients with appropriate patient educational brochure, patient card and/or equivalent tool

- Safety advice relevant to all patients
    - Description and management of thrombocytopenia including incidence rates from clinical studies
    - Description and management of cardiac failure
    - Local country specific arrangements for a prescription for pomalidomide to be dispensed
    - That any unused capsules should be returned to the pharmacist at the end of the treatment
    - That the patient should not donate blood during treatment (including during dose interruptions) and for at least 7 days following discontinuation of Pomalidomide Zentiva

- 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 prescriber should take if unsure

- Safety advice for women of childbearing potential
    - The need to avoid foetal exposure
    - Description of the PPP
    - Need for effective contraception (even if the woman has amenorrhoea) and definition of effective contraception
    - That if she needs to change or stop using her method of contraception she should inform:
        - The physician prescribing her contraception that she is on pomalidomide
        - The physician prescribing pomalidomide that she has stopped or changed her method of contraception
    - Pregnancy test regime
        - Advice on suitable tests

        - Before commencing treatment
        - During treatment based on method of contraception
        - After finishing treatment
    - Need to stop Pomalidomide Zentiva 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 the man has had a vasectomy)
        - During Pomalidomide Zentiva treatment
        - For at least 7 days following final dose
    - That he should not donate semen or sperm during treatment (including during dose interruptions) and for at least 7 days following discontinuation of Pomalidomide Zentiva treatment
    - That if his partner becomes pregnant whilst he is taking Pomalidomide Zentiva or shortly after he has stopped taking Pomalidomide Zentiva he should inform his treating doctor immediately
- Requirements in the event of pregnancy
    - Instructions to stop Pomalidomide Zentiva immediately upon suspicion of pregnancy, if female patient
    - Need to refer patient 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 immediately
    - Pregnancy reporting form

- Local contact details for reporting adverse reactions

Educational Brochures for patients

The Educational brochures for patients should be of 3 types:

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

All educational brochures for patients should contain the following elements:

- That pomalidomide is teratogenic in animals and is expected to be teratogenic in humans
- That pomalidomide may cause thrombocytopenia and the need for regular blood tests
- Description of the patient card and its necessity
- Guidance on handling Pomalidomide Zentiva for patients, caregivers and family members
- National or other applicable specific arrangements for a prescription for Pomalidomide Zentiva to be dispensed
- That the patient must not give Pomalidomide Zentiva to any other person
- That the patient should not donate blood during treatment (including during dose interruptions) and for at least 7 days after discontinuation of Pomalidomide Zentiva treatment
- That the patient should tell their doctor about any adverse events
- That any unused capsules should be returned to the pharmacist at the end of the treatment

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
- The need for effective contraception and definition of effective contraception
- That if she needs to change or stop using her method of contraception she should inform:
    - The physician prescribing her contraception that she is on pomalidomide
    - The physician prescribing pomalidomide that she has stopped or changed her method of contraception
- Pregnancy test regime
    - Before commencing treatment
    - During treatment (including dose interruptions), at least every 4 weeks except in case of confirmed tubal sterilisation
    - After finishing treatment
- The need to stop Pomalidomide Zentiva 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 and not using effective contraception (even if the man has had vasectomy)
    - During Pomalidomide Zentiva treatment (including dose interruptions)
    - 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 treatment (including during dose interruptions) and for at least 7 days following discontinuation of Pomalidomide Zentiva treatment

Patient Card or equivalent tool

The patient card shall contain the following elements:
- Verification that appropriate counselling has taken place
- Documentation of childbearing potential status
- Check box (or similar) which physician ticks to confirm that patient is using effective contraception (if woman of childbearing potential)
- Pregnancy test dates and results

Risk Awareness Forms

There should be 3 types of risk awareness forms:
- Women of childbearing potential
- Women of non-childbearing potential
- Male patient

All risk awareness forms should contain the following elements:
- teratogenicity warning
- patients receive the appropriate counselling prior to treatment initiation
- affirmation of patient understanding regarding the risk of pomalidomide and the PPP measures
- date of counselling
- patient details, signature and date
- prescriber name, signature and date
- aim of this document i.e. as stated in the PPP: "The aim of the risk awareness form is to protect patients and any possible foetuses by ensuring that patients are fully informed of and understand the risk of teratogenicity and other adverse reactions associated with the use of pomalidomide. It is not a

contract and does not absolve anybody from his/her responsibilities with regard to the safe use of the product and prevention of foetal exposure."

Risk awareness forms for women of childbearing potential should also include:
- Confirmation that the physician has discussed the following:

    - the need to avoid foetal exposure
    - that if she is pregnant or plans to be, she must not take pomalidomide
    - that she understands the need to avoid pomalidomide during pregnancy and to apply effective contraceptive measures without interruption, at least 4 weeks before starting treatment, throughout the entire duration of treatment, and at least 4 weeks after the end of treatment
    - that if she needs to change or stop using her method of contraception she should inform:
        - the physician prescribing her contraception that she is taking Pomalidomide Zentiva
        - the physician prescribing Pomalidomide Zentiva that she has stopped or changed her method of contraception
    - of the need for pregnancy tests i.e. before treatment, at least every 4 weeks during treatment and after treatment
    - of the need to stop Pomalidomide Zentiva immediately upon suspicion of pregnancy
    - of the need to contact their doctor immediately upon suspicion of pregnancy
    - that she should not share the medicinal product with any other person
    - that she should not donate blood during treatment (including during dose interruptions) and for at least 7 days following discontinuation of Pomalidomide Zentiva

    - that she should return the unused capsules to the pharmacist at the end of treatment

Risk awareness forms for women with no childbearing potential should also include:
- Confirmation that the physician has discussed the following:
    - that she should not share the medicinal product with any other person
    - that she should not donate blood during treatment (including during dose interruptions) and for at least 7 days following discontinuation of Pomalidomide Zentiva
    - that she should return the unused capsules to the pharmacist at the end of treatment

Risk awareness forms for male patients should also include:

- Confirmation that the physician has discussed the following:
    - the need to avoid foetal exposure
    - that pomalidomide is found in semen and the need to use condoms if sexual partner is pregnant or is a WCBP not on effective contraception (even if the man has had a vasectomy)
    - that if his partner becomes pregnant, he should inform his treating doctor immediately and always use a condom
    - that he should not share the medicinal product with any other person
    - that he should not donate blood or semen during treatment (including during dose interruptions) and for at least 7 days following discontinuation of Pomalidomide Zentiva
    - that he should return the unused capsules to the pharmacist at the end of treatment

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

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

   - Prior to prescribing (where appropriate, and in agreement with the National Competent Authority, dispensing) all healthcare professionals who intend to prescribe (and dispense) Pomalidomide Zentiva are provided with an Educational Healthcare Professional's Kit containing the following:
     - Educational Healthcare Professional brochure
     - Educational brochures for patients
     - Patient card Risk awareness forms
     - Information on where to find latest Summary of Product Characteristics (SmPC)

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 medicinal product.
3. The MAH should agree the contents of the Educational Healthcare Professional's Kit with the National Competent Authority in each Member State prior to launch of the medicinal product and ensure that the materials contain the key elements as described below.
4. The MAH should agree on the implementation of the controlled access programme in each Member State.

Key elements to be included

Educational Healthcare Professional's Kit

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

Educational Healthcare Professional brochure

- Brief background on pomalidomide
- Maximum duration of treatment prescribed
  - 4 weeks for women with childbearing potential
  - 12 weeks for men and women without childbearing potential
- The need to avoid foetal exposure due to teratogenicity of pomalidomide in animals and the expected teratogenic effect of pomalidomide in humans
- Guidance on handling the blister or capsule of Pomalidomide Zentiva for healthcare professionals and caregivers
- Obligations of the healthcare professionals who intend to prescribe or dispense Pomalidomide Zentiva
  - Need to provide comprehensive advice and counselling to patients
  - That patients should be capable of complying with the requirements for the safe use of Pomalidomide Zentiva
  - Need to provide patients with appropriate patient educational brochure, patient card and/or equivalent tool

- Safety advice relevant to all patients
  - Description and management of thrombocytopenia including incidence rates from clinical studies
  - Description and management of cardiac failure
  - Local country specific arrangements for a prescription for pomalidomide to be dispensed
  - That any unused capsules should be returned to the pharmacist at the end of the treatment

- That the patient should not donate blood during treatment (including during dose interruptions) and for at least 7 days following discontinuation of Pomalidomide Zentiva

- 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 prescriber should take if unsure

- Safety advice for women of childbearing potential

  - The need to avoid foetal exposure
  - Description of the PPP
  - Need for effective contraception (even if the woman has amenorrhoea) and definition of effective contraception

  - That if she needs to change or stop using her method of contraception she should inform:
    - The physician prescribing her contraception that she is on pomalidomide
    - The physician prescribing pomalidomide that she has stopped or changed her method of contraception
  - Pregnancy test regime
    - Advice on suitable tests
    - Before commencing treatment
    - During treatment based on method of contraception
    - After finishing treatment
  - Need to stop Pomalidomide Zentiva 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 the man has had a vasectomy)
    - During Pomalidomide Zentiva treatment
    - For at least 7 days following final dose
  - That he should not donate semen or sperm during treatment (including during dose interruptions) and for at least 7 days following discontinuation of Pomalidomide Zentiva treatment
  - That if his partner becomes pregnant whilst he is taking Pomalidomide Zentiva or shortly after he has stopped taking Pomalidomide Zentiva he should inform his treating doctor immediately
- Requirements in the event of pregnancy
  - Instructions to stop Pomalidomide Zentiva immediately upon suspicion of pregnancy, if female patient
  - Need to refer patient 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 immediately
  - Pregnancy reporting form

- Local contact details for reporting adverse reactions

Educational Brochures for patients

The Educational brochures for patients should be of 3 types:

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

All educational brochures for patients should contain the following elements:

- That pomalidomide is teratogenic in animals and is expected to be teratogenic in humans
- That pomalidomide may cause thrombocytopenia and the need for regular blood tests
- Description of the patient card and its necessity
- Guidance on handling Pomalidomide Zentiva for patients, caregivers and family members
- National or other applicable specific arrangements for a prescription for Pomalidomide Zentiva to be dispensed
- That the patient must not give Pomalidomide Zentiva to any other person
- That the patient should not donate blood during treatment (including during dose interruptions) and for at least 7 days after discontinuation of Pomalidomide Zentiva treatment
- That the patient should tell their doctor about any adverse events
- That any unused capsules should be returned to the pharmacist at the end of the treatment

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

<u>Brochure for women patients with childbearing potential</u>

- The need to avoid foetal exposure
- Description of the PPP
- The need for effective contraception and definition of effective contraception
- That if she needs to change or stop using her method of contraception she should inform:
    - The physician prescribing her contraception that she is on pomalidomide
    - The physician prescribing pomalidomide that she has stopped or changed her method of contraception
- Pregnancy test regime
    - Before commencing treatment
    - During treatment (including dose interruptions), at least every 4 weeks except in case of confirmed tubal sterilisation
    - After finishing treatment
- The need to stop Pomalidomide Zentiva immediately upon suspicion of pregnancy
- The need to contact their doctor immediately upon suspicion of pregnancy

<u>Brochure for male patients</u>

- The need to avoid foetal exposure
- The need to use condoms if sexual partner is pregnant or a WCBP and not using effective contraception (even if the man has had vasectomy)
    - During Pomalidomide Zentiva treatment (including dose interruptions)
    - 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 treatment (including during dose interruptions) and for at least 7 days following discontinuation of Pomalidomide Zentiva treatment

<u>Patient Card or equivalent tool</u>

The patient card shall contain the following elements:

- Verification that appropriate counselling has taken place
- Documentation of childbearing potential status
- Check box (or similar) which physician ticks to confirm that patient is using effective contraception (if woman of childbearing potential)
- Pregnancy test dates and results

Risk Awareness Forms

There should be 3 types of risk awareness forms:
- Women of childbearing potential
- Women of non-childbearing potential
- Male patient

All risk awareness forms should contain the following elements:
- teratogenicity warning
- patients receive the appropriate counselling prior to treatment initiation
- affirmation of patient understanding regarding the risk of pomalidomide and the PPP measures
- date of counselling
- patient details, signature and date
- prescriber name, signature and date
- aim of this document i.e. as stated in the PPP: "The aim of the risk awareness form is to protect patients and any possible foetuses by ensuring that patients are fully informed of and understand the risk of teratogenicity and other adverse reactions associated with the use of pomalidomide. It is not a contract and does not absolve anybody from his/her responsibilities with regard to the safe use of the product and prevention of foetal exposure."

Risk awareness forms for women of childbearing potential should also include:
- Confirmation that the physician has discussed the following:

    - the need to avoid foetal exposure
    - that if she is pregnant or plans to be, she must not take pomalidomide
    - that she understands the need to avoid pomalidomide during pregnancy and to apply effective contraceptive measures without interruption, at least 4 weeks before starting treatment, throughout the entire duration of treatment, and at least 4 weeks after the end of treatment
    - that if she needs to change or stop using her method of contraception she should inform:
        - the physician prescribing her contraception that she is taking Pomalidomide Zentiva
        - the physician prescribing Pomalidomide Zentiva that she has stopped or changed her method of contraception
    - of the need for pregnancy tests i.e. before treatment, at least every 4 weeks during treatment and after treatment
    - of the need to stop Pomalidomide Zentiva immediately upon suspicion of pregnancy
    - of the need to contact their doctor immediately upon suspicion of pregnancy
    - that she should not share the medicinal product with any other person
    - that she should not donate blood during treatment (including during dose interruptions) and for at least 7 days following discontinuation of Pomalidomide Zentiva

    - that she should return the unused capsules to the pharmacist at the end of treatment

Risk awareness forms for women with no childbearing potential should also include:
- Confirmation that the physician has discussed the following:
    - that she should not share the medicinal product with any other person

- that she should not donate blood during treatment (including during dose interruptions) and for at least 7 days following discontinuation of Pomalidomide Zentiva
- that she should return the unused capsules to the pharmacist at the end of treatment

Risk awareness forms for male patients should also include:

- Confirmation that the physician has discussed the following:
  - the need to avoid foetal exposure
  - that pomalidomide is found in semen and the need to use condoms if sexual partner is pregnant or is a WCBP not on effective contraception (even if the man has had a vasectomy)
  - that if his partner becomes pregnant, he should inform his treating doctor immediately and always use a condom
  - that he should not share the medicinal product with any other person
  - that he should not donate blood or semen during treatment (including during dose interruptions) and for at least 7 days following discontinuation of Pomalidomide Zentiva
  - that he should return the unused capsules to the pharmacist at the end of treatment

These conditions fully reflect the advice received from the PRAC.