14 December 2023
EMA/21354/2024
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Pomalidomide Viatris

International non-proprietary name: Pomalidomide

Procedure No. EMEA/H/C/006195/0000

## 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

| | |
|---|---|
| API | Active pharmaceutical ingredient |
| AR | Assessment report |
| ASM | Active substance manufacturer |
| ASMF | Active substance master file = drug master file |
| BDL | Below the limit of detection |
| CHMP | Committee for Medicinal Products for Human Use |
| CoA | Certificate of analysis |
| EEA | European Economic Area |
| EMA | European Medicines Agency |
| ERA | Environmental risk assessment |
| FP | Finished product |
| FPM | Finished product manufacturer |
| HPLC | High performance liquid chromatography |
| IPC | In-process control test |
| GC | Gas chromatography |
| GCP | Good clinical practice |
| GLP | Good laboratory practice |
| LoA | Letter of access |
| $LogK_{ow}$ | n-octanol/water partition coefficient |
| LoD | Limit of detection |
| LoQ | Limit of quantitation |
| LoQ | List of questions |
| MAH | Marketing authorisation holder |
| MS | Mass spectroscopy |
| NfG | Note for guidance |
| NLT | Not less than |
| NMT | Not more than |
| PBT | Persistence bioaccumulation toxicity |
| vPvB | Very persistent very bioaccumulative |
| $PEC_{surfacewater}$ | Predicted environmental concentration |
| Ph. Eur. | European Pharmacopoeia |
| PIL | Patient information leaflet |
| RH | Relative humidity |
| RSD | Relative standard deviation |
| SmPC | Summary of Product Characteristics |
| UV | Ultra-violet |
| XRD | X-Ray diffraction |

Not all abbreviations may be used.

# 1. Background information on the procedure

## *1.1. Submission of the dossier*

The applicant Viatris Limited submitted on 2 March 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Pomalidomide Viatris, 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 15 September 2022.

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) of Directive 2001/83/EC.

The applicant applied for the following indications:

> Pomalidomide Viatris 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 Viatris 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 1 mg, 2 mg, 3 mg, 4 mg hard capsule
- Marketing authorisation holder: Bristol-Myers Squibb Pharma EEIG
- Date of authorisation: 05-08-2013
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/13/850/001-008

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

- Product name, strength, pharmaceutical form: Imnovid 1 mg, 2 mg, 3 mg, 4 mg hard capsule
- Marketing authorisation holder: Bristol-Myers Squibb Pharma EEIG
- Date of authorisation: 05-08-2013

- Marketing authorisation granted by:
  - Union

Marketing authorisation number: EU/1/13/850/001-008

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 1 mg, 2 mg, 3 mg, 4 mg hard capsule
- Marketing authorisation holder: Bristol-Myers Squibb Pharma EEIG
- Date of authorisation: 05-08-2013
- Marketing authorisation granted by:
  - Union
  - Marketing authorisation number: EU/1/13/850/001-008
- Bioavailability study number(s): POMA-CAZ-1003 and POMA-CAZ-1004

## *1.3. Information on paediatric requirements*

Not applicable

## *1.4. Information relating to orphan market exclusivity*

### 1.4.1. 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.

### 1.4.2. Derogation(s) from market exclusivity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant submitted a claim addressing the following derogation laid down in Article 8.3 of the same Regulation:

- the holder of the marketing authorisation for the original orphan medicinal product has given their consent to the applicant to submit an application before the orphan designation of the reference product Imnovid expired. Imnovid was withdrawn from the Community register of orphan medicinal products in August 2023 at the end of the 10-year period of market exclusivity. The derogation was applicable at the time of validation.

## *1.5. Scientific advice*

The applicant did not seek scientific advice from the CHMP.

## *1.6. Steps taken for the assessment of the product*

The Rapporteur and appointed by the CHMP were:

Rapporteur: Simona Badoi

| | |
|---|---|
| The application was received by the EMA on | 2 March 2023 |
| The procedure started on | 23 March 2023 |
| The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on | 12 June 2023 |
| The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on | 28 June 2023 |
| The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on | 20 July 2023 |
| The applicant submitted the responses to the CHMP consolidated List of Questions on | 06 September 2023 |
| 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 | 17 October 2023 |
| The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on | 26 October 2023 |
| The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on | 9 November 2023 |
| The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on | 15 November 2023 |
| 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 | 29 November 2023 |
| 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 Viatris on | 14 December 2023 |
| The CHMP adopted a report on similarity of Pomalidomide Viatris with Kyprolis (carfilzomib), Imnovid (pomalidomide), Ninlaro (ixazomib), Farydak (panobinostat), Darzalex (daratumumab), Blenrep (belantamab mafodotin), Abecma (idecabtagene vicleucel), Carvykti (Ciltacabtagene autoleucel) and Talvey (talquetamab) on (Appendix on similarity). | 14 December 2023 |
| The CHMP adopted a report on derogations applicable to similar orphan products for Pomalidomide Viatris on | 14 December 2023 |

# 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.

Reference product is Imnovid 1 mg, 2 mg, 3 mg, 4 mg capsule, hard, registered by Bristol-Myers Squibb Pharma EEIG. The community marketing authorisation of the reference product was granted on 05 August 2013 under number EU/1/13/850/001-008.

The applicant has developed Pomalidomide Viatris 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 Viatris 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 Viatris 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 or 4 mg of pomalidomide as active substance.

Other ingredients are:

Capsule contents: starch, pregelatinised, silica, colloidal anhydrous, magnesium stearate, mannitol, and croscarmellose sodium.

Capsule shell: gelatin (1mg, 2 mg, 3 mg, 4 mg), titanium dioxide (E171) (1mg, 2 mg, 3 mg, 4 mg), ferric oxide red (E172) (1mg, 2 mg), ferric oxide yellow (E172)( (1mg, 2 mg, 3 mg) , and indigo carmine (E132) (1mg, 2 mg, 3 mg, 4 mg)

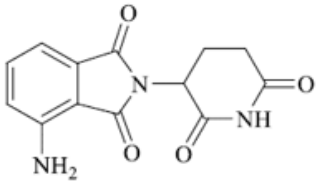
Printing ink: shellac, black iron oxide (E172), propylene glycol, and ammonium hydroxide.

The product is available in PVC/PCTFE-Aluminium blister pack or PVC/PCTFE-Aluminium unit dose blister pack as described in section 6.5 of the SmPC.

### 2.2.2. Active substance

***General information***

The chemical name of pomalidomide is (RS)-4-Amino-2-(2,6-dioxo-piperidin-3-yl)-isoindoline-1,3-dione, *or* 4-Amino-2-(2,6-dioxo-3-piperidinyl)-1*H*-isoindole-1,3(2*H*)- dione, *or* 3-amino-*N*-(2,6-dioxo-3-piperidyl) phthalimide, *or* 1,3-dioxo-2-(2,6-dioxopiperidin-3-yl)-4-aminoisoindoline corresponding to the molecular formula $C_{13}H_{11}N_3O_4$. It has a relative molecular mass of 273.25 g/mol and the structure:




Pomalidomide

**Figure 1 Pomalidomide structure**

Pomalidomide was characterised by UV, IR, $^{1}H$ NMR, $^{13}C$ NMR, mass spectroscopy, elemental analysis, powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC) and thermo gravimetric analysis (TGA).

The active substance is a non- hygroscopic yellow to greenish yellow powder, freely soluble in dimethyl sulfoxide (DMSO), soluble in N, N-Dimethylformamide and insoluble in water.

The active substance has one chiral centre and a test for specific optical rotation confirms that the active substance is a racemic mixture.

Polymorphism has been observed for the active substance. Pomalidomide is reported to exist in crystalline forms with different names *viz.* Form-A, I, B, M and O in literature. Based on further review, the PXRD crystalline pattern is found to be similar for all the reported literature polymorphs [Forms-A, I, B, M and O] and shows characteristic angular positions (2θ) in the same regions, thus confirming that the pomalidomide exists in a single crystalline form.

***Manufacture, characterisation and process controls***

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 3 main stages using well defined starting materials with acceptable specifications.

A brief narrative description of the synthesis in the applicant's part of the ASMF was provided.

Adequate in-process controls were applied during the synthesis.

The specifications and control methods for intermediate products, starting materials and reagents are presented.

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.

In relation to residual solvents, general information is provided. Class-II and III solvents are used in the last step of the synthesis and controlled in the API specification. No class-1 solvents are used in the synthesis.

Elemental analysis as per ICH Q3D was performed on three active substance batches. Class 1 and 2A elemental impurities have been considered. Results for all elements are below detection limit,. The description of the ICP-MS method and validation data are provided.

A major objection was initially raised about the risk of nitrosamine formation in the active substance and the applicant provided with an updated assessment for the possible formation of nitrosamine taking into consideration manufacturing process, key starting materials, all raw materials, catalysts, solvents, intermediates, by-products of different stages, recovered solvent. The justification was accepted, it was considered that there was no risk of potential formation of nitrosamine impurities in the active substance.

The active substance is packaged in transparent LDPE bag, twisted and tied with a plastic fastener. The polyethylene bag containing the active substance is then inserted in black polyethylene bag and tied with plastic fastener. Both these bags are put into the triple laminated aluminum bag and heat sealed. These bags are further packed in HDPE container, closed with plastic lid having rubber gasket, followed by locking ring and metal sealed and labelled. The polythene bags comply with Commission Regulation (EU) 10/2011, as amended.

***Specification***

The active substance specification includes tests for appearance (visual), solubility, identification (IR, HPLC, PXRD), water content (KF), sulfated ash (Ph. Eur.), specific optical rotation (Ph. Eur.), related substance (HPLC), assay (HPLC), residual solvents (HSGC), and palladium content (ICP-MS).

A HPLC method is used to control the related substances of active substance. The proposed limits are in line with ICH Q3A (reporting threshold 0.05%, identification threshold 0.10%, qualification threshold 0.15%).

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) 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 proposed manufacturer stored in the intended commercial package for up to 36 months under long term conditions (25±2°C, 60±5% RH) and for up to 6 months under accelerated conditions (40±2°C, 75±5% RH) according to the ICH guidelines were provided.

The following parameters were tested: appearance, identification, water content, related substances, and assay.

Stability data for the accelerated and long-term conditions reveals that there is no significant changes in any of the parameters. The level of impurities has been reported within a specification limit. Long-term stability studies will be continued to confirm the retest period.

Results on stress conditions at solution state degradation (acid hydrolysis, base hydrolysis, oxidation, and heat degradation), and solid state degradation (photostability, heat and humidity stressed) were also provided. The stress stability data shows that pomalidomide is stable under stress condition.

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 48 months without 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:

1 mg strength: blue opaque cap and light yellow opaque body, imprinted with 'VIATRIS' over 'PM1' in black ink. The gelatin hard capsule is approximately 15.9 mm in length.

2 mg strength: blue opaque cap and light orange opaque body, imprinted with 'VIATRIS' over 'PM2' in black ink. The gelatin hard capsule is approximately 15.9 mm in length.

3 mg strength: blue opaque cap and light green opaque body, imprinted with 'VIATRIS' over 'PM3' in black ink. The gelatin hard capsule is approximately 18 mm in length.

4 mg strength: blue opaque cap and light blue opaque body, imprinted with 'VIATRIS' over 'PM4' in black ink. The gelatin hard capsule is approximately 18 mm in length.

The purpose of the pharmaceutical development studies was to develop an essentially similar generic version of the reference medicinal product, Imnovid. The developed product should be suitable for production scale batches and exhibit reproducible results. The product demonstrated acceptable stability performance in the proposed marketing pack(s).

Pomalidomide represents a BCS class IV compound. Sufficient data has been provided to characterise the solubility, polymorphism and particle size of the active substance.

Binary mixtures of the active substance with the selected excipients were prepared with different ratios and exposed to extreme conditions. The results of the active substance-excipient compatibility studies show that there was no significant change in the physical appearance and related substances of the binary mixtures. Hence, based on physical appearance and related substances data, it can be concluded the active substance is compatible with all the specified excipients.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. The used colourants comply with directive (EU) No. 231/2012. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

Based on the characterisation of reference medicinal product, it was determined that the test product should have the following attributes: the product has to be formulated as immediate release capsules which are meant to administer orally having pomalidomide as the active substance and it has to be pharmaceutical equivalent to the reference medicinal product, the formulation should have comparable dissolution profile with reference product, and the product should have satisfactory pharmaceutical stability.

Pomalidomide capsules were developed with dry granulation, milling, blending and encapsulation process.

Biowaiver of strengths 2 mg and 3 mg has been applied. The product meets the general requirements according to Guideline on Investigation on Bioequivalence (CHMP/EWP/QWP/1401/98 Rev 01). Based on the information provided biowaiver can be accepted.

There is no difference in the unit composition of the formulation used in the clinical study and the formulation intended for commercial supplies, but a different commercial description with changes in the composition of the capsule shell cap is proposed (different colour). Same manufacturing process

was used for batches used in bio-equivalence study, manufacturing process validation study and stability studies.

The selection of the apparatus, agitation speed, volume and dissolution media were justified. In order to assess the ability of the selected dissolution method to discriminate between good (bio-equivalent) and bad formulation, dissolution studies have been performed on different batches taken with slightly modified composition and manufacturing process and the discriminatory power of the dissolution method has been demonstrated.

The primary packaging is PVC/PCTFE-Aluminium blister pack. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

***Manufacture of the product and process controls***

The manufacturing process consists of 9 main steps: blending, sifting, blending and sifting, pre-compaction blending, compaction, mixing, sifting and blending of extra granular material, final blending and encapsulation.

Major steps of the manufacturing process have been validated by a number of studies in three consecutive batches per strength. 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.

***Product specification***

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form: description (visual), dimension, identification (HPLC, HPLC with PDA detector), uniformity of dosage units (Ph. Eur.), assay (HPLC), dissolution (HPLC), related substances (HPLC), water (KF), microbiological test (Ph. Eur), and colour identification.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on 3 batches per strength using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed (as requested as MO) 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 "European Medicines Regulatory Network approach for the implementation of the CHMP Opinion pursuant to Article 5(3) of Regulation (EC) Nº 726/2004 for nitrosamine impurities in human medicines (EMA/425645/2020). The active substance manufacturer has also performed confirmatory testing on possible nitrosamine impurities. All results were consistently below the limit of detection. Overall, the LC-MS/MS method was adequately validated and representative chromatograms with better resolution were resubmitted. Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the finished product. Therefore, no additional 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 are 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.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

***Stability of the product***

Stability data from 3 commercial scale batches per strength of finished product stored for up to 12 months under long term conditions (25 ± 2°C / 60 ± 5% RH) and for up to 6 months under accelerated conditions (40 ± 2°C / 75 ± 5% RH) according to the ICH guidelines were provided. The batches of the finished product are identical to those proposed for marketing except the composition of the capsule shell and were packed in the primary packaging proposed for marketing.

The bulk pack is proposed for holding the finished product before packaging the finished product into marketable pack. A simulated bulk pack has been studied at accelerated and long-term stability conditions. The packaging of the simulated bulk pack is essentially similar, differing only in dimensions with respect to bulk pack.

Samples were tested for description, assay, dissolution, related substances, water and microbiological test.

All tested parameters were compliant with the acceptance criteria set in the specification at long term and accelerated conditions. No trends can be observed (no decreasing of assay and no increasing of impurities and water).

In addition, 1 batch per strength were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The study results indicated that there were no out of specification results observed for quality aspects. Thus, it can be concluded that the finished product is not photosensitive.

Based on available stability data, the proposed shelf-life of 2 years without special storage conditions as stated in the SmPC (section 6.3) are 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.

During evaluation 3 major objections were raised by the CHMP in relation to starting materials and risk assessment of nitrosamines in the active substance and finished product which were resolved by provision of additional information.

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 manner. Data has been presented to give reassurance on viral/TSE safety.

### 2.2.6. Recommendation(s) for future quality development

No 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

A Phase I environmental risk assessment (ERA) has been submitted. The predicted environmental concentration ($PEC_{surfacewater}$), calculated using European disease prevalence data is below the action limit of 0.01 µg/L. Thus, a Phase II environmental fate and effects analysis is not deemed necessary. The n-octanol/water partition coefficient (log $K_{ow}$) was determined by the classical stir-flask method at three different n-octanol/water phase ratios (0.5, 1, and 2) (Szabo et al, 2021). Log $K_{ow}$ of pomalidomide is clearly below the action limit value of 4.5, thus screening according to the EU Technical Guidance is not required. Based on the log $K_{ow}$ value, pomalidomide is not considered PBT or vPvB.

### 2.3.3. Discussion on non-clinical aspects

The applicant has not performed non-clinical studies. Non-clinical data are submitted from published literature data. This is reasonable and acceptable since pomalidomide is a well-known active substance. Grounds for not providing new non-clinical data are adequately justified.

A brief statement that based on finished product shelf-life specifications, related substances in the drug product are within the ICH Q3B(R2) qualification level has been included in the non-clinical overview.

All excipients are compendial and there are no toxicological concerns raised with regard to either the impurities or the excipients. Please, follow the Quality Assessment Report for more details.

The SPC sections 4.6 and 5.3 are in line with those for the innovator Imnovid, 1 mg, 2 mg, 3 mg, 4 mg capsule, hard, registered by Bristol-Myers Squibb Pharma EEIG and are therefore acceptable.

The ERA submitted by the applicant is acceptable.

### 2.3.4. Conclusion on the non-clinical aspects

Data presented are acceptable from the non-clinical point of view. There are no objections to the approval of Pomalidomide Viatris 1 mg, 2 mg, 3 mg, 4 mg capsule, hard 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 two bioequivalence studies with cross-over design under fasting conditions using the 1 and 4 mg strengths respectively. These studies were the pivotal studies for this application. The SmPC is in line with the SmPC of the reference product.

No formal scientific advice by the CHMP was given for this medicinal product. For the clinical assessment Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1) in its current version 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.

According to the applicant the methods and procedures followed in this project were as per study protocol and the SOPs. Please see the following tables for the various companies/CRO, their role in the conduct of the bioequivalence study and the Regulatory authorities which inspected the sites.

The signed statements declaring compliance with ICH-GCP, GLP requirements, EMA guidelines, the ethical requirements of Directive 2001/20/EC and 'Declaration of Helsinki' have been provided by the applicant.

The quality assurance documents and monitoring reports have been provided. The applicant has also provided a list of GCP inspections at the clinical and analytical sites.

***Exemption***

A strength biowaiver is requested for Pomalidomide 2 mg and 3 mg hard capsules.

The applicant made reference to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1 – January. 2010) according to which the following are claimed to be fulfilled:

a) All the strengths of Pomalidomide Capsules (2 mg, 3 mg and 4 mg) are manufactured by the same manufacturer at the same manufacturing site using same manufacturing process.

b) The qualitative composition of the different strengths is the same.

c) The composition of the strengths (2mg, 3mg and 4 mg) is quantitatively proportional, i.e., the ratio between the amount of each excipient to the amount of active substance is the same for all the strengths.

d) Similar *in-vitro* dissolution data confirm the adequacy of waiving 2 mg and 3 mg from *in vivo* bioequivalence testing (see also below).

e) Pomalidomide exhibits a linear pharmacokinetic profile. Pomalidomide exhibits linear, time-dependent pharmacokinetic (see also text below).

For criteria a-c see also the quality part of this report which is in line with the claims posed.

**Linear Pharmacokinetics of Pomalidomide (criterion e):** Following oral administration, pomalidomide undergoes biphasic disposition. The systemic exposure (AUC) of pomalidomide increases in an approximately linear and dose proportional manner based on the EPAR and the SmPC of Imnovid. Following multiple doses, pomalidomide has an accumulation ratio of 27 to 31% on AUC.

**Comparative dissolution profiles (criterion d)**

Comparative dissolution profiles of the applicant's Pomalidomide 1 mg, 2 mg, 3 mg and 4 mg capsules and EU reference product Imnovid (Pomalidomide) 1 mg, 2 mg, 3 mg and 4 mg hard capsules (manufactured by Celgene Distribution B.V; MA Holder- Bristol-Myers Squibb Pharma EEIG) were generated in different dissolution media i.e. 0.1N hydrochloric acid, pH 4.5 acetate buffer and pH 6.8 phosphate buffer, as per below table.

**Table 1: Parameters of the comparative dissolution testing**

| **Parameter** | **Conditions** |
|---|---|
| Dissolution media | 0.1N Hydrochloric acid<br>pH 4.5 acetate buffer<br>pH 6.8 Phosphate buffer |
| Dissolution apparatus | Type – II (Paddle with sinker) |
| RPM | 50 |
| Volume | 900 mL |
| Temperature | 37°C ± 0.5°C |
| Sampling time (for profile study only) | 10 min, 15 min, 20 min, 30 min, 45 min and 60 min |
| Surfactant | - |

The dissolution methodology using the Ph. Eur. paddle apparatus was in accordance with the Guideline on the investigation of bioequivalence and no surfactant was used. The use of a helix sinker with different dimensions than the ones described in Ph.Eur was justified by the applicant.

*Comparison of test formulations*

The applicant provided comparative dissolution data between the test formulations. Dissolution testing has been conducted at three different pH medium 0.1 N HCl, 4.5 acetate buffer and 6.8 Phosphate buffer between the pomalidomide 2 mg, 3 mg and 4 mg (batch used for the bioequivalence study) and the results are found be similar.

At pH medium 0.1 N HCl and 6.8 phosphate buffer the applicant has not calculated the f2 similarity factor since more than 85% of the labelled amount of the drug was released within 15 minutes, based on average value for dissolution from 12 units, therefore, at these pH medium dissolution profiles can be accepted as similar, without further mathematical calculations. At pH medium 4.5 acetate buffer, f2 was >50. For the f2 similarity evaluation only the first time points have been considered :10 min, 15 min and 20 min and the last (defined as the first point when dissolution of either formulations reaches or exceeds 85%) excluding any later sampling times.

Based on the above, the applicant claims:

- that the similarity of the dissolution profiles of 2 mg, 3 mg and 4 mg strengths of the test formulation at pH medium 4.5 acetate buffer is considered demonstrated. Therefore, the provided dissolution data between the additional strengths and the biobatch can support the requested strength based biowaiver.
- the *in vivo* bioequivalence study requirement for strengths 2 mg and 3 mg can be waived because all the biowaiver criteria have been fulfilled as mentioned in CPMP guideline on the Investigation of Bio-equivalence – CPMP/EWP/QWP/1401/98- Rev 01 – January 2010
- the bioequivalence study results of pomalidomide 4 mg capsules can be extended to pomalidomide 2 mg and 3 mg capsules.

Note: The composition of the 1 mg strength deviates from the proportionality when compared to the other strengths and cannot be exempted based on the above. Therefore an additional bioequivalence study was performed with the 1 mg strength.

*Comparison of test formulations against the reference product*

Comparative dissolution profiles were also provided at three different pH medium 0.1 N HCl, 4.5 acetate buffer and 6.8 Phosphate buffer of the applicant's Pomalidomide 1 mg and 4 mg capsules (manufactured by Mylan Laboratories Limited, India) and EU reference product Imnovid (pomalidomide) 1 mg and 4 mg hard capsules (manufactured by Celgene Distribution B.V; MA Holder-Bristol-Myers Squibb Pharma EEIG), tested in the bioequivalence studies were also generated.

- For the 1 mg strength,
    - at pH medium 0.1 N HCl as more than 85% drug was released in 15 minutes for reference and test product, dissolution profiles can be accepted as similar, without further mathematical calculations.
    - At pH medium 4.5 acetate buffer and 6.8 phosphate buffer, more than 85% drug was released in 15 minutes only for test product and the f2 similarity factor could not be calculated as the CHMP guideline requirement of minimum 3 time points with not more than 1 time point above 85% drug release was not fulfilled.

Thus, the similarity of the dissolution profiles between the test and the reference products at 1 mg strength used in the bioequivalence study cannot be confirmed using the f2 statistics at pH medium 4.5 acetate buffer and 6.8 phosphate buffer.

- For the 4 mg strength,
    - at pH medium 0.1 N HCl more than 85% drug was released in 15 minutes only for test product and the f2 similarity factor could not be calculated as the CHMP guideline requirement of minimum 3 time points with not more than 1 time point above 85% drug release was not fulfilled.
    - At pH 4.5 acetate buffer, faster drug release was observed for the test product as compared to the reference product, during initial time points, and f2 was 46.93, below 50, based on the selection of the first three time points 10 min, 15 min and 20 min.

The exclusion of the later time points was based on the last sampling time considered for f2 calculation to be the one when either of the products reaches 85% or more dissolved.

- At pH 6.8 phosphate buffer more than 85% drug was released in 15 minutes only for test product and the f2 similarity factor could not be calculated as the CHMP guideline requirement of minimum 3 time points with not more than 1 time point above 85% drug release was not fulfilled.

Thus, the conditions for f2 calculation were not able to be fulfilled in either pH media for the 4 mg strength (see also discussion).

**Tabular overview of clinical studies**

To support the application, the applicant has submitted 2 bioequivalence studies. Due to the deviation of the 1 mg formulation from the proportional composition, the applicant performed two bioequivalence studies with the highest and the lowest strengths, i.e., 1 mg and 4 mg, respectively, which is in line with the Guideline on the investigation of bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1.

**Table 2: 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 | Project No. POMA-CAZ-1003 | Clinical Study Report, PK Report, Adverse Event Listing, CRFs and Individual Subjects **(5.3.1.2)** Bioanalytical Report **(5.3.1.4)** Literature References **(5.4)** | The objective of this study was to investigate the bioequivalence of Pomalidomide 1 mg hard capsules of Mylan Laboratories Limited, India with Imnovid® (Pomalidomide) 1mg Hard Capsules of Celgene Europe B.V, in healthy adult male human subjects and to monitored the adverse events and ensured the safety of the subjects. | Single dose fasting oral bioequivalence study of Pomalidomide 1 mg hard capsules of Mylan Laboratories Limited, India with Imnovid® (Pomalidomide) 1mg Hard Capsules of Celgene Europe B.V., in healthy adult male human subjects. | **Test Drug(T):** Pomalidomide Capsules 1 mg 1x1 mg **Reference Drug (R):** Imnovid® 1 mg Pomalidomide hard capsules 1x1 mg | **Planned:** 32 subjects +additional subjects may be enrolled **Enrolled :** 32 subjects (subject numbers 01-32) + 02 additional subjects (Standby-I &Standby-II) **Dosed :** Period-1: 32 subjects Period-2: 30 subjects **Withdrawn:** 02 subjects (Subject numbers 08 & 15 did not report to the facility for period-2 check in. **Completed :** 30 Subjects completed study criteria. **Bio-sample analyzed:** 30 subjects **Pharmacokinetic and statistical data analyzed:** 30 subjects | Healthy, adult, human subjects | Single-dose | Complete; Abbreviated |

| 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 | Project No. POMA-CAZ-1004 | Clinical Study Report, PK Report, Adverse Event Listing, CRFs and Individual Subjects **(5.3.1.2)** Bioanalytical Report **(5.3.1.4)** Literature References **(5.4)** | The objective of this study was to investigate the bioequivalence of Pomalidomide 4 mg hard capsules of Mylan Laboratories Limited, India with Imnovid® (Pomalidomide) 4 mg Hard Capsules of Celgene Europe B.V, in healthy adult male human subjects and to monitored the adverse events and ensured the safety of the subjects. | Single dose fasting oral bioequivalence study of Pomalidomide 4 mg hard capsules of Mylan Laboratories Limited, India with Imnovid® (Pomalidomide) 4 mg Hard Capsules of Celgene Europe B.V., in healthy adult male human subjects. | **Test Drug(T):** Pomalidomide Capsules 4 mg 1x4 mg Oral **Reference Drug (R):** Imnovid® 4 mg Pomalidomide hard capsules 1x4 mg Oral | **Planned:** 32 subjects +additional subjects may be enrolled **Enrolled :** 32 subjects (subject numbers 01-32) **Dosed :** Period-1: 32 subjects Period-2: 32 subjects **Withdrawn:** 01 subject (Subject number 24 was withdrawn from the study after 33.00 hours post dose in period-2 due to personal reason.) **Completed :** 31 Subjects completed study criteria. **Bio-sample analyzed:** 32 subjects **Pharmacokinetic and statistical data analyzed:** 32 subjects | Healthy, adult, human subjects | Single-dose | Complete; Abbreviated |

## 2.4.2. Clinical pharmacology

### *2.4.2.1. Pharmacokinetics*

***Study*** POMA-CAZ-1003***:*** Single dose fasting oral bioequivalence study of Pomalidomide 1 mg hard capsules with Imnovid (pomalidomide) 1mg Hard Capsules of Celgene Europe B.V., in healthy adult male human subjects.

***Methods***

- **Study design**

This was a single oral dose, open labelled, randomised, two-period, two-treatment, two-sequence, cross over study investigating the bioequivalence of Pomalidomide 1 mg hard capsules to Celgene Europe B.V. of Imnovid (pomalidomide) 1mg hard capsules following administration of a single, oral dose of 1 mg (1 x 1 mg) in 32 normal, healthy, adult male human subjects under fasting conditions.

**Duration of the study:**

Clinical Phase:

29 Oct 2022 to 07 Nov 2022 (from Check-in period 1 to period 2 last sample collection date)

Period 1: 30 Oct 2022 (First subject treated) – 31 Oct 2022 (Last subject visit)

Period 2: 06 Nov 2022 – 07 Nov 2022

Analytical Phase:

09 Nov 2022 – 16 Nov 2022

**Study data:**

Study protocol version number 00 dated 02 August 2022 and Informed Consent Form dated 02 August 2022 have been approved by Independent Ethics Committee on 17 September 2022. Minor protocol

amendment from 27 October 2022, which consisted of administrative changes and typographical error, was approved by Independent Ethics Committee on 28 October 2022.

The Final Clinical Study Report is dated 01 February 2023.

Allocation of treatment for each subject in each study period was carried out per the randomisation schedule.

The test and reference products were administered according to the randomisation schedule. The test product was administered as a single, oral dose of 1 mg (1 x 1 mg) with 240 ± 2 mL of ambient temperature water. The reference product was administered as a single, oral dose of 1 mg (1 x 1 mg) with 240 ± 2 mL of ambient temperature water. Immediately after dose administration, each subject's oral cavity and hands were checked to confirm medication and fluid consumption. Dose administration was completed as scheduled.

All subjects fasted overnight and were dosed at the 0.00 hour, at the rate of 32 subjects in 02 dosing stations every 02 minute(s) beginning at 07:30 hours and ending at 08:00 hours. On the day of dosing, subjects received a standard low-fat meal approximately 4.00, 8.00 & 12.00 hours (with a grace period of + 45 minutes) post dose. Water was not permitted for 1 hour before dosing and until 1 hours after dosing but was allowed at all other times. A 7 day washout separated dosing in each period.

During each study period, 20 blood samples were collected (5 mL each) from each subject by indwelling catheter using tubes containing K3EDTA as an anticoagulant. Blood samples were collected within 120 minutes prior to dose administration (0.00 hour) and after dose administration at 0.33, 0.67, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 7.00, 8.00, 10.00, 12.00, 18.00, 24.00 and 36.00 hours. Plasma samples were collected over 36 hours. Frequent sampling was planned around expected tmax. Considering the median tmax occurring 1 to 4 hours post-dose, the sampling period and the sampling scheme seems adequate to estimate the primary PK parameters of pomalidomide.

Since AUC0-t covers at least 80% of AUC0-∞, the sampling schedule covers the plasma concentration time curve long enough. Tmax was not observed in any subject at the first sample time point.

The median plasma t1/2 following of pomalidomide is approximately 9.5 hours in healthy subjects, thus the washout period of 07 days is more than 5 half-lives of the active substance.

Approximately 200 mL of blood was collected from each subject for pharmacokinetic samples over the course of the study. The actual time at which each blood sample was collected was recorded by clinical staff.

Samples were collected by indwelling catheter, inverted 5-10 times immediately after collection, and immediately placed in an ice bath. The samples were then centrifuged under refrigeration (4°C ± 3°C) at approximately 4000 ± 100 rpm for 10 minutes. The plasma was returned to an ice bath and transferred into the following labelled polypropylene tubes: 12x75 mm polypropylene RIA vial tube.

Each plasma sample was divided into two (2) aliquots (Aliquot 1 was contained 1.5 mL of plasma and Aliquot 2 was contained 1.0 mL of plasma) and frozen within 90 minutes after the start of centrifugation at -70°C or colder with an acceptable operating range within -55°C to -85°C. Plasma samples were frozen in an upright position in a freezer unit with a set point of -70º C or colder with an acceptable operating range within -55°C to -85°C until shipment for analysis.

Upon completion of the study, a total of 1240 plasma samples of aliquot 1 of 2 and 1240 plasma samples of aliquot 2 of 2 were shipped on 08 Nov 2022 and 09 Nov 2022 respectively to the bioanalytical facility for analysis.

- **Test and reference products**

Pomalidomide Viatris 1 mg has been compared to Imnovid 1 mg manufactured by Celgene Europe B.V..

**Table 3: Test and reference product information (POMA-CAZ-1003)**

| Product Characteristics | Test Product (T) | Reference Product (R) |
|---|---|---|
| Name | Pomalidomide Capsules 1 mg | Imnovid® 1 mg Pomalidomide |
| Strength | 1 mg | 1mg |
| Dosage Form | Hard Capsules | Hard Capsules |
| Batch number | 2023873 | C2392EC |
| Batch Size | 1,25,000 Capsules | Not available |
| Measured Content(s) (% of Label Claim) | 102.5 % w/w | 100.3 % w/w |
| Commercial Batch Size | Not available | Not available |
| Manufacturing Date | JUN.2022 | - |
| Expiry Date | MAY 2024 | 06/2024 |
| Location of Certificate of Analysis | 5312-compar-ba-be-stud-rep, Appendix-16.2.5 (Certificate of Analysis) | 5312-compar-ba-be-stud-rep, Appendix-16.2.5 (Certificate of Analysis) |
| Member State where the reference product is purchased from: | Not applicable | Netherlands |
| This product was used in the following trials: | Study nos.: POMA-CAZ-1003 | Study nos.:POMA-CAZ-1003 |

The size of the bio batch for Pomalidomide 1 mg hard capsules corresponded to the size proposed for industrial batches and is 125,000 hard capsules.

- **Population(s) studied**

A total of 32 plus 02 additional (standby – I & standby – II) healthy adult male subjects (Asian race, mean age 34 ± 6.9 years, mean height of 166.4 ± 6.78 -centimetre, mean weight of 71.85 ± 10.924 kg/$m^2$, mean BMI 25.9 ± 3.27 kg/$m^2$ have been enrolled in the clinical trial.

32 subjects have been dosed in Period I and 30 subjects in Period II. Out of 32 subjects, 30 subjects completed both study periods of the clinical phase of the study and have been included in the statistical analysis. Two subjects have not report to the facility for period 2 check-in.

The demographic characteristics of the 30 subjects who constituted the PK population of the study are: mean age 35 ± 6.6 years, mean height of 166.6 ± 6.69 -centimetre, mean weight of 72.23 ± 11.078 kg/$m^2$, mean BMI 26.0 ± 3.15 kg/$m^2$ have been enrolled in the clinical trial.

**Table 4** presents the number of subjects who were randomised per each treatment sequence and post-randomisation discontinuations, if any, that occurred over the course of the study.

**Table 4: Summary of subject disposition**

| | Sequence | | Total |
|---|---|---|---|
| | TR | RT | |
| Subjects Randomized | 16 | 16 | 32 |
| Subjects Successfully Completed study criteria | 15 | 15 | 30 |
| Subjects Who Withdrew Consent | 01* | 01* | 02 |
| Subjects Discontinued by the Investigator | 00 | 00 | 00 |

Treatment T: Pomalidomide Capsules 1 mg (Batch No.: 2023873)
Treatment R: Imnovid 1 mg Pomalidomide hard capsules (batch No.: C2392EC)
* Subject numbers 08 & 15 did not report to the facility for period 2 check-in.

**Table 5: List of discontinued/withdrawn subjects**

| Subject Number | Period | Reason for Discontinuation |
|---|---|---|
| 08 | 2 | Subject number 08 did not report to the facility for period-2 check-in.<br>Date: 05 Nov 2022<br>Time: 21:14 hours<br>Last Treatment Received: Treatment R |
| 15 | 2 | Subject number 15 did not report to the facility for period-2 check-in.<br>Date: 05 Nov 2022<br>Time: 21:28 hours<br>Last Treatment Received: Treatment T |

Treatment T: Pomalidomide Capsules 1 mg (Batch No.: 2023873)
Treatment R: Imnovid® 1 mg Pomalidomide hard capsules (Batch No.: C2392EC)

Main inclusion criteria:

Subjects who met the following criteria were included in the study:

- Normal healthy adult male human subjects, age between 18 to 45 years old.
- Body mass index of ≥18.5 kg/m2 and ≤30.0 kg/$m^2$ and weight ≥ 50.00 kg.
- Healthy according to the laboratory results and physical examination, performed within 21 days prior to the commencement of the dosing in Period-1.
- Subject whose clinical laboratory values were within normal limits or clinically nonsignificant as determined by physician or principal investigator to be of no clinical significance.
- Adequate venous access in both arms for the collection of a number of blood samples during the study
- Subject willing to follow the protocol requirements and comply with protocol restrictions.
- Had normal ECG, Chest X-ray and vital signs.
- Non-smoker and Non-alcoholic.
- Subject with normal range of PT and aPTT.
- Subject with CrCl value more than 60 mL/min.
- Subject able to communicate effectively and willing to provide informed consent.

Exclusion criteria:
Any history of allergy or hypersensitivity to pomalidomide and / or other related drugs.

- Positive test result for hepatitis B surface antigen (HBs Ag), hepatitis C virus antibody (HCV Ab) or HIV-1 antibody or HIV Type 2 (HIV-2) antibody (HIV Ab) or VDRL / syphilis.
- The study drug was contraindicated for medical reasons.

- Any history or presence of significant haematological (including history of toxic or idiosyncratic granulocytopenia/agranulocytosis), cardiovascular, pulmonary, hepatic, renal, gastrointestinal, endocrine, dermatological, neurological, psychiatric diseases or disorders.
- Any history of bleeding disorders, peptic ulcer diseases, haemorrhoids, wounds/ ulcers.
- Subject having any history of blood clots in arteries, veins, and lungs, heart attack and stroke happened in the past.
- History or presence of drug abuse in the past one year.
- Difficulty in swallowing tablets/capsules.
- Any history of difficulty in donating blood.
- Had clinically significant abnormal values of laboratory parameters.
- Blood pressure is < 100/70 and > 129/79 millimetres of mercury (Systolic blood pressure/Diastolic blood pressure).
- Pulse rate less than 60 beats / minute and more than 100 beats / minute.
- Subject with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption.
- Used of any prescription or over-the-counter (OTC), herbal, medications other than hormonal contraceptive or hormone replacement therapy within the 14 days prior to the initial administration of study medication.
- Any clinically significant illness during 3 months before screening.
- Participation in a drug research study/donation of blood within past 90 days.
- Consideration by the investigator, for any reason that the subject is an unsuitable candidate to receive study drug.
- Subject positive for alcohol test (by using Urine/Blood sample), urine screen for drugs of abuse test [Cannabinoids (Marijuana/Tetra Hydro Cannabinoids-THC), Cocaine, Opiates (morphine), Amphetamines, Barbiturates and Benzodiazepines] at the time of each period check-in was excluded from the study.

No female subjects have been included in the study.

Determination of the sample size

Based on reported and in-house data on Pomalidomide the maximum intra subject variability observed among primary pharmacokinetic parameters was found to be ~15%.

Hence, considering the CV of 15% the following estimates were considered for the computation of sample size:

T/R ratio = 90.0 to 111.0 %

Maximum Intra-Subject C.V (%) = ~15%

Significance Level = 5%

Power = 90%

Bioequivalence Limits = 80 – 125%

Based on the above estimate, a sample size of 28 subjects were sufficient to establish bioequivalence between formulations. However, taking into account the withdrawal & drop-out subjects, a sample size of 32 subjects were considered for the study.

- **Analytical methods**

The analytical samples were stored at -70±10ºC until analysed.

A validation of the analytical technique was provided. The analytical method validation report No. BL-MVR-361 was enclosed and dated 05 November 2019.

**Validation of the analytical method**

Method validation of pomalidomide in human plasma was carried out as per Method Validation Protocol No. BL-MVP-361.

Analytical Method: LC-MS/MS with Liquid-Liquid Extraction, Biological Matrix – plasma

The method was validated for system suitability, sensitivity, autosampler carryover, selectivity, matrix effect, linearity, reinjection reproducibility, effect of Haemolysed plasma, effect of lipemic plasma, effect of concomitant medication, recovery, within batch precision and accuracy, between batch precision and accuracy, dilution integrity, ruggedness, stability of the analyte in plasma, bench top stability of the spiked quality control samples, autosampler stability of the quality control samples up to 97 hours 57 minutes at 5±3°C, wet extract stability at room temperature, wet extract stability at refrigerator temperature (2-8°C), dry extract stability of the spiked quality control samples at room temperature, long-term stability of the stock solution and working solutions up to 6 days 21 hours and 20 minutes at 2-8°C.

The method was amended twice. The purpose of Addendum 01 of the method validation as presented in the report No. BL-MV-361/A01 from 03 January 2020 was to perform the long-term stability in matrix for analyte in human K3EDTA plasma, i.e., partial validation. Long-term stability was validated for a period of 34 days at 28 ± 5°C, freeze and thaw stability at -70 ± 15°C.

**Addendum – 02 (Partial validation)**

The method was partially validated for freeze thaw stability for 5 cycles (34 days) at -28 ± 5°C and -70 ± 15°C, bench top stability of the spiked quality control samples at room temperature for 17 hours, autosampler stability of the processed quality control samples for 95 hours and 09 minutes at 5 ± 3°C, wet extract stability at room temperature of the spiked quality control samples for 23 hours and 30 minutes, dry extract stability of the spiked quality control samples at room temperature for 23 hours and 33 minutes, wet extract stability at refrigerator temperature for 95 hours 24 minutes, stability of the analyte in the whole blood at room temperature for 03 hours and 55 minutes and at -28 ± 5°C for 03 hours and 35 minutes. The method validation report No. BL-MV-361/A02 from 24 January 2023 was submitted.

Within study validation

The plasma samples of subjects have been analysed using a validated LC-MS/MS analytical method (SOP No. BL020-12, BL073-02 and BL074-01) using Pomalidomide d4 as internal standard, with ZORBAX XDB Phenyl (75 x 4.6 mm) 3.5 µm column. The analyte and internal standard were extracted from aliquot of 400 µL $K_3$EDTA human plasma using liquid-liquid phase extraction method.

Quantitation was determined by peak area ratio method. Calibration curves were obtained using a linear equation with $1/x^2$ as weighting factor for peak area ratio (analyte/ internal standards) versus the nominal concentration of the calibration standards. Study sample concentrations were obtained by interpolation from the run defined calibration curve. Calibration range used during the study was 0.400 ng/mL to 149.726 ng/mL.

Blood samples were collected into $K_3$EDTA tubes and centrifuged under refrigeration (4°C ± 3°C) at 4000±100 RPM for 10 minutes to separate plasma. The plasma samples were frozen and retained at -70±10°C until assay. Samples were packed on dry ice for shipment to bioanalytical laboratory. The bioanalysis was carried out between 09 November 2022 and 16 November 2022.

Ten non-zero calibration standards and six levels of QC samples were used. The QC concentrations were 0.400 ng/mL (LLOQ), 1.088 ng/mL (LQC), 4.327 ng/mL (MQC3), 8.654 ng/mL (MQC2), 68.037 ng/mL (MQC1) and 113.395 ng/mL (HQC) for study sample analysis.

The maximum study sample storage period from first day of sample collection 30 October 2022 to the last day of sample analysis completion 16 November 2022 was 18 days at -70±10°C, which is covered by the long-term stability period at -28 ± 5°C and -70 ± 15°C of 34 days.

**Sample Information**

**Table 6: Sample analysis of study No POMA'CAZ'1003**

| Analyte | Pomalidomide |
|---|---|
| Total numbers of collected samples | 1240 |
| Total number of samples with valid results | 1200 |
| Total number of reassayed samples[1,2] | 15 |
| Total number of analytical runs[1] | 16 |
| Total number of valid analytical runs[1] | 16 |
| Incurred sample reanalysis | |
| Number of samples | 120 |
| Percentage of samples where the difference between the two values was less than 20% of the mean for chromatographic assays or less than 30% for ligand binding assays | 117 (97.50%) |

[1] Without incurred samples, Investigation and P&A

[2] Due to other reasons than not valid run

According to the protocol, all concentration values below the lower limit of quantification (BLOQ) will be set to zero.

Incurred sample reanalysis was conducted on 120 samples (10%) from a total of 1200 samples with valid results. 97.5% (117/120) of concentrations obtained by reanalysis were found within their initial value.

Reanalysis of study samples: A total of 1240 samples were analysed in 16 analytical runs (without ISR and Precision & Accuracy), with one (1) analytical run rejected.

15 samples (1.25%) were re-assayed due to improper/inconsistent Internal Standard Area – 14 samples and poor chromatography – one sample.

- **Pharmacokinetic variables**

The pharmacokinetic parameters have been computed by using Phoenix WinNonlin version 8.0 or higher version for Pomalidomide through non compartmental method.

Per protocol, the primary pharmacokinetic variables for assessment of bioequivalence are Cmax and AUC0-t for Pomalidomide. The secondary pharmacokinetic parameters are: AUC0-∞, Tmax, Kel, T1/2 and AUC %Extrap_obs.

Pharmacokinetic parameters have been calculated from individual plasma concentrations of 30 subjects out of 32 enrolled who completed both periods of the clinical trial successfully, as two subjects were discontinued (subject numbers 08 & 15 were did not report to the facility for period 2 check-in) from the study.

- **Statistical methods**

Statistical analyses were performed on the pharmacokinetic parameters using the General Linear Models Procedure (PROC GLM) of SAS Software (version 9.4). The parameters: Tmax, Kel and t1/2

were analysed statistically using the non-transformed data. The natural log transformed parameters: ln-AUC0-t and ln-Cmax were also analysed.

Two protocol deviations have been reported during the study. Two subject number 08 and 15 did not report to the facility for period-2 check-in and have been excluded from the PK and statistical analysis.

All concentration values below the lower limit of quantification (BLOQ) have been set to zero, concentration obtained as 0, <0. No Peak will be reported as Zero for all pharmacokinetic and statistical calculations. Any missing samples will be reported as 'M' and have not been included for pharmacokinetic and statistical analysis.

Individual and Mean plasma concentration vs. time plots were generated on both Linear and Semi-log axis for Pomalidomide.

The summary statistics (for relevant pharmacokinetic parameters) have been computed and reported for both test and reference products of Pomalidomide.

The In-transformed pharmacokinetic parameters Cmax and AUC0-t of Pomalidomide have been subject to Analysis of Variance (ANOVA).

ANOVA model included terms for Sequence, formulation, Period and Subject (Sequence) as fixed effects. The sequence effect has been tested using the Subject (Sequence) effect as an error term.

The period and treatment effects have been tested at 5% level of significance and sequence effects have been tested at 10% level of significance.

Two one-sided tests for bioequivalence and 90% confidence intervals for the ratio of least squares mean between drug formulations have been calculated, for In-transformed data of Cmax and AUC0-t of Pomalidomide. The power of the test to detect 20% difference between test and reference products has been computed and reported for Pomalidomide.

Ratio of least squares means of test and reference products have been computed for ln-transformed pharmacokinetic parameters Cmax and AUC0-t of Pomalidomide.

Ratio analysis have been reported for In-transformed pharmacokinetic parameters Cmax and AUC0-t of Pomalidomide.

Intra-subject variability have been computed for In-transformed pharmacokinetic parameters Cmax and AUC0-t of Pomalidomide.

*Criteria for conclusion of bioequivalence*

The acceptance criteria for bioequivalence were that the entire confidence intervals for the difference of means of Ln-transformed Cmax and AUC0-t should be within 80.00% -125.00%. Standard bioequivalence criteria are proposed for the primary pharmacokinetic endpoints Cmax and AUC0-t which is adequate.

***Results***

**Table 7: Pharmacokinetic parameters for pomalidomide (non-transformed values)**

| Pharmacokinetic parameter | Test | | Reference | |
|---|---|---|---|---|
| | **Arithmetic mean geometric mean** | **SD CV%** | **Arithmetic mean geometric mean** | **SD CV%** |
| $AUC_{(0-t)}$ (ng*hr/mL) | 147.222<br>142.026 | ±40.9267<br>27.8% | 144.118<br>131.643 | ±41.6358<br>28.9% |

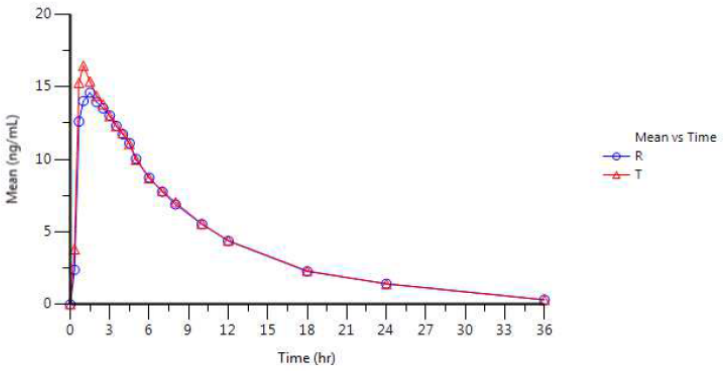
| Pharmacokinetic parameter | Test | | Reference | |
|---|---|---|---|---|
| | Arithmetic mean<br>geometric mean | SD<br>CV% | Arithmetic mean<br>geometric mean | SD<br>CV% |
| $AUC_{(0-\infty)}$<br>(ng*hr/mL) | 155.945<br>150.386 | ±43.4780<br>27.9% | 152.246<br>138.493 | ±43.9268<br>28.9% |
| $C_{max}$ (ng/mL) | 18.830<br>18.940 | ±4.1310<br>21.9% | 16.742<br>16.347 | ±3.7542<br>22.4% |
| $T_{max}$* (hr) | 1.000 | 0.670 – 4.500 | 1.000 | 0.670 – 4.000 |
| $AUC_{0-t}$ | 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 8: Statistical analysis for pomalidomide (ln-transformed values)**

| Pharmacokinetic parameter | Geometric Mean Ratio Test/Reference | Confidence Intervals | CV%* |
|---|---|---|---|
| $AUC_{(0-t)}$ | 102.30 | 97.53 - 107.31 | 10.92% |
| $C_{max}$ | 112.48 | 102.87 - 123.00 | 20.56% |
| * estimated from the Residual Mean Squares | | | |

**Figure 2: Linear and semi log plot of mean pomalidomide plasma concentration**

**Linear Plot:**



**Semi Log Plot:**

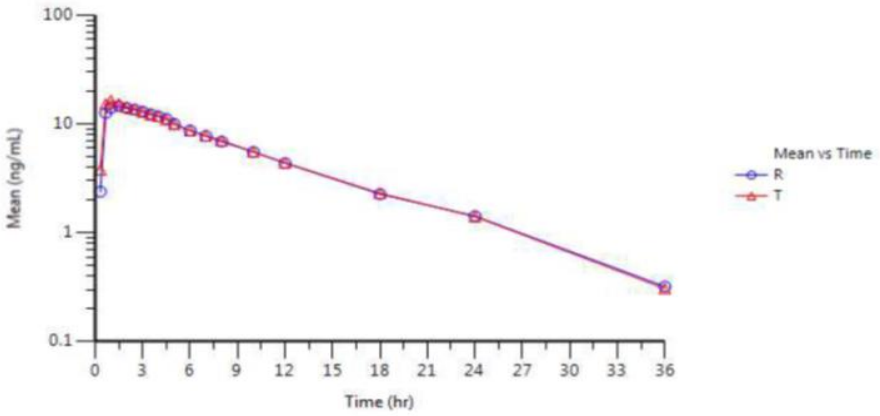



**Table 9: P-values from ANOVA table**

| Pharmacokinetic Parameters | p-value for Treatment/Formulation | p-value for period | p-value for Sequence |
|---|---|---|---|
| $AUC_{0-t}$ (hr.ng/mL) | 0.4249 | 0.1176 | 0.5273 |
| $C_{max}$ (ng/mL) | 0.0333 | 0.8159 | 0.3412 |

Source: Sub Section 16.2.6.2.1 of Section 16.2.6.2 of Appendix 16.2.6.

The pharmacokinetic parameter data including the confidence intervals and point estimates presented by the applicant are in line with the acceptance criteria of the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr – revised 2010).

Linear and semi-log plots have been submitted.

The 90% confidence intervals for the ln-transformed values for AUC0-t and Cmax were within the 80.00 – 125% limit and are considered acceptable.

Cmax was not observed in any subject at the first sample time point and pre-dose concentration has not been detected in any subject. The extrapolated AUC was not higher than 20% in any subject, and thus the blood sampling schedule up to 36 h was defined adequately.

The applicant does not report any statistically significant sequence, period or treatment effect for AUC0-t and does not report any statistically significant sequence and period effect for Cmax. A significant treatment effect was reported for Cmax, however, the bioequivalence was demonstrated

- **Safety data**

Safety parameters were assessed in 32 subjects. No AEs have been reported in the study.

There were no clinically significant findings in the vital signs assessment or the laboratory tests in any of the subjects in the study.

Administrations of test and reference products to healthy subjects were safe and well tolerated.

## Study Protocol Number: POMA-CAZ-1004

**Study Title:** Single dose fasting oral bioequivalence study of Pomalidomide 4 mg hard capsules with Imnovid (Pomalidomide) 4 mg Hard Capsules of Celgene Europe B.V., in healthy adult male human subjects.

**Methods**

- **Study design**

This was a single oral dose, open labelled, randomised, two-period, two-treatment, two-sequence, crossover study investigating the bioequivalence of Pomalidomide 4 mg hard capsules to. Imnovid (Pomalidomide) 4 mg Hard Capsules (Celgene Europe B.V) following administration of a single, oral dose of 4 mg (1 x 4 mg) in 32 normal, healthy, adult male human subjects under fasting conditions.

**Duration of the study:**

Clinical Phase:

Period 1: 31 Oct 2022 – 02 Nov 2022

Period 2: 13 Nov 2022 - 15 Nov 2022

Analytical Phase:

17 Nov 2022 - 24 Nov 2022

**Study data:**

Study protocol version number 00 dated 02 August 2022 and Informed Consent Form version number 00 dated 02 August 2022 have been approved by Independent Ethics Committee on 17 Sep 2022 and 28 Oct 2022, respectively. The protocol amendment 00 dated 27 Oct 2022, which consisted of administrative change and typographical error, was approved by Independent Ethics Committee on 28 Oct 2022.

The Final Clinical Study Report is dated 17 February 2023.

Allocation of treatment for each subject in each study period was carried out per the randomisation schedule.

The study was initiated with 32 healthy subjects. All subjects checked into the clinical facility on the day prior to dosing. Check-in occurred at least 10.50 hours prior to dose administration for each study period. On study day 1, each subject received either a single, oral dose of 4 mg (1 x 4 mg) of the test product, Pomalidomide Capsules 4 mg or a single oral dose of 4 mg (1 x 4 mg) of the reference product, Imnovid 4 mg Pomalidomide hard capsules.

The test and reference products were administered according to the randomisation schedule. Subjects were dosed in 02 dosing stations at 02-minute intervals during all study periods. Drug administration was assisted with 240 ± 2 mL of ambient temperature water. Immediately after dose administration, each subject’s oral cavity and hands were checked to confirm medication and fluid consumption. Dose administration was completed as scheduled.

Dosing occurred following an overnight fast of at least 10.00 hours. Following a 13-day washout period, all subjects returned to the clinical facility to be dosed with the alternative treatment as per the randomisation. During each study period, 20 blood samples were collected (5 mL each) from each

subject by indwelling catheter using tubes containing K3EDTA as an anticoagulant. In each study period, blood samples were collected within 120 minutes prior to dose administration (0.00 hour) and post-dose at study hours 0.33, 0.67, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 7.00, 8.00, 10.00, 12.00, 18.00, 24.00 and 36.00 hours. The subjects were allowed to leave the clinical facility after 36.00 hours post dose. Plasma samples were collected over 36 hours. Frequent sampling was planned around expected $t_{max}$. Considering the median $t_{max}$ occurring 1 to 4 hours post-dose, the sampling period and the sampling scheme seems adequate to estimate the primary PK parameters of pomalidomide.

Since $AUC_{0-t}$ covers at least 80% of $AUC_{0-\infty}$, the sampling schedule covers the plasma concentration time curve long enough. $T_{max}$ was not observed in any subject at the first sample time point.

The median plasma t1/2 following of pomalidomide is approximately 9.5 hours in healthy subjects, thus the washout period of 13 days is more than 5 half-lives of the active substance.

Approximately 200 mL of blood was collected from each subject for pharmacokinetic samples over the course of the study. The actual time at which each blood sample was collected was recorded by clinical staff.

Samples were collected by indwelling catheter, inverted 5-10 times immediately after collection, and immediately placed in an ice bath. The samples were then centrifuged under refrigeration (4°C±3°C) at approximately 4000±100 rpm for 10 minutes. The plasma was returned to an ice bath and transferred into the following labelled polypropylene tubes: 12x75 mm polypropylene RIA vial tube.

Each plasma sample was divided into two (2) aliquots (Aliquot 1 was contained 1.5 mL of plasma and Aliquot 2 was contained 1.0 mL of plasma) and frozen within 90 minutes after the start of centrifugation at -70°C or colder with an acceptable operating range within -55°C to -85°C.

Upon completion of the study, a total of 1279 plasma samples of aliquot 1 of 2 and 1279 plasma samples of aliquot 2 of 2 were shipped on 16 Nov 2022 and 17 Nov 2022 respectively to the bioanalytical facility for analysis.

**Test and reference products**

**Table 10: Test and reference product information [POMA-CAZ-1004]**

| Product Characteristics | Test Product (T) | Reference Product (R) |
|---|---|---|
| Name | Pomalidomide Capsules 4 mg | Imnovid® 4 mg Pomalidomide |
| Strength | 4 mg | 4 mg |
| Dosage Form | Hard Capsules | Hard Capsules |
| Batch number | 2023937 | C2421AA |
| Batch Size | 62500 Capsules | Not available |

| | | |
|---|---|---|
| Measured Content(s) (% of Label Claim) | 101.8 % w/w | 98.4 % w/w |
| Commercial Batch Size | Not available | Not available |
| Manufacturing Date | JUN.2022 | - |
| Expiry Date | MAY 2024 | 10/2024 |
| Location of Certificate of Analysis | 5312-compar-ba-be-stud-rep, Appendix-16.2.5 (Certificate of Analysis) | 5312-compar-ba-be-stud-rep, Appendix-16.2.5 (Certificate of Analysis) |
| Member State where the reference product is purchased from: | Not applicable | Netherlands |
| This product was used in the following trials: | Study no.: POMA-CAZ-1004 | Study no.: POMA-CAZ-1004 |

The size of the bio batch for Pomalidomide 4 mg hard capsules corresponded to the size proposed for industrial batches and is 62,500 hard capsules.

The choice of the reference product is appropriate. According to the documentation provided, the Member State of source for the reference product used in the BE study is the Netherlands.

The batch size of the test product used in the bioequivalence study is 62500 hard capsules, which is in accordance with the Bioequivalence Guideline requirements. The proposed commercial batch size for 4 mg strength is identical with the bio-batch size of 62500 hard capsules and that is acceptable, although a commercial batch size up to 10-fold larger than the batch size used for bioequivalence evaluation could be allowed.

Certificates of analysis have been provided and the difference in content of active substance between reference and test product is less than 5.0%.

- **Population(s) studied**

A total of 32 plus healthy adult male subjects (Asian race, mean age 32 ± 5.6 years, mean height of 167.9 ± 6.37-centimetre, mean weight of 70.38 ± 9.636 kg/m2, mean BMI 25.0 ± 2.16 kg/m2 have been enrolled in the clinical trial.

All the subjects enrolled into the study fulfilled the inclusion and exclusion criteria. All the subjects were of normal health based on general physical examination and laboratory tests.

None of the subjects had any relevant or significant previous medical history that could affect the study results.

The study population was chosen according to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 01 – January 2010).

The sample size was calculated based on the following estimates: T/R ratio = 90.0 to 111.0 %, maximum Intra-Subject C.V (%) = ~15%, significance Level = 5%, power = 90%, bioequivalence limits = 80 – 125%, which is considered adequate. Therefore, the number of the subjects included in the study is found sufficient.

32 subjects have been enrolled in the study and 31 subjects completed the study. One subject was discontinued (subject number 24 was withdrawn after 33.00 hours post dose in period-2 due to personal reason) from the study. 32 subjects have been considered for PK and statistical analysis, according to the approved protocol.

- **Analytical methods**

The analytical samples were stored at -70±10ºC until analysed.

A validation of the analytical technique was provided. The analytical method validation report No. BL-MVR-361 was enclosed and dated 05 November 2019.

**Validation of the analytical method**

Method validation of pomalidomide in human plasma was carried out as per Method Validation Protocol No. BL-MVP-361.

Analytical Method: LC-MS/MS with Liquid-Liquid Extraction, Biological Matrix – plasma

The same validated analytical method was used as for the quantitation of pomalidomide from human plasma samples collected in study POMA-CAZ-1003. For the validation of the analytical method, please see the part of the assessment report regarding the analytical methods for study POMA-CAZ-1004.

The bioanalytical method is acceptable and has been validated according to the Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/09). However, because the ICH M10 guideline on bioanalytical method validation and study sample analysis, came into effect on the 21 January 2023, one OC has been raised, as outlined below.

Statement on GLP compliance was provided. Handling of samples was adequate.

Within-study validation

The plasma samples of subjects have been analysed using a validated LC-MS/MS analytical method (SOP No. BL020-12, BL073-02 and BL074-01) using pomalidomide d4 as internal standard, with ZORBAX XDB Phenyl (75 x 4.6 mm) 3.5 µm column. The analyte and internal standard were extracted from aliquot of 400 µL K3EDTA human plasma using liquid-liquid phase extraction method.

Quantitation was determined by peak area ratio method. Calibration curves were obtained using a linear equation with 1/x2 as weighting factor for peak area ratio (analyte/ internal standards) versus the nominal concentration of the calibration standards. Study sample concentrations were obtained by interpolation from the run defined calibration curve. Calibration range used during the study was 0.400 ng/mL to 149.726 ng/mL.

Blood samples were collected into K3EDTA tubes and centrifuged under refrigeration (4°C ± 3°C) at 4000±100 RPM for 10 minutes to separate plasma. The plasma samples were frozen and retained at -70±10°C until assay. Samples were packed on dry ice for shipment to bioanalytical laboratory. The bioanalysis was carried out between 15 November 2022 and 24 November 2022.

Ten non-zero calibration standards and six levels of QC samples were used. The QC concentrations were 0.400 ng/mL (LLOQ), 1.088 ng/mL (LQC), 4.327 ng/mL (MQC3), 8.654 ng/mL (MQC2), 68.037 ng/mL (MQC1) and 113.395 ng/mL (HQC) for study sample analysis.

The real sample storage period i.e., time between the dates of first blood collection to last sample analysis was 24 days and was fully covered by the long-term stability at 34 days (at -70±10°C) as determined during the validation.

The calibration standards of the in-study validation were acceptable.

The LLOQ of the bioanalytical method 0.400 ng/mL was below 1/20 of the Cmax (arithmetic means for pomalidomide: test 56.814 ng/mL, reference 56.702 ng/mL) and was adequate to detect any relevant carry-over effect between the treatment periods.

Reasons for reanalysis of pomalidomide samples (N=10; 0.78 %) were provided and considered acceptable.

Incurred sample reanalysis was evaluated to demonstrate that the results obtained from study sample analysis had been reproducible. Incurred sample reanalysis was conducted on 128 samples (10% of the first 1000 samples plus 10% of the number of samples that exceeded 1000 samples) from a total of 1279 samples with valid results. 100.00% (128/128) of concentrations obtained by reanalysis were found within their initial value, which is in accordance with the ICH Guideline M10 on bioanalytical method validation and study sample analysis (EMA/CHMP/ICH/172948/2019).

Chromatograms for approximately 20% of the subjects are presented and are acceptable. However, according to ICH M10 guideline on bioanalytical method validation and study sample analysis, that came into effect on the 21 January 2023, 100% of chromatograms have been requested for the conducted BE studies. Chromatograms of all runs for method validation and subject sample analysis have been provided as requested and are acceptable. All chromatograms were integrated automatically.

- **Pharmacokinetic Variables**

The pharmacokinetic parameters have been computed by using Phoenix WinNonlin version 8.0 or higher version for Pomalidomide through non compartmental method.

Per protocol, the primary pharmacokinetic variables for assessment of bioequivalence are Cmax and AUC0-t for Pomalidomide. The secondary pharmacokinetic parameters are: AUC0-∞, Tmax, Kel, T1/2 and AUC %Extrap_obs. The pharmacokinetic parameters are adequate for a bioequivalence trial with an immediate-release formulation.

Pharmacokinetic parameters have been calculated from individual plasma concentrations of all 32 subjects enrolled, according to the protocol. One subject has been discontinued (subject number 24

was withdrawn after 33.00 hours post dose in period-2 due to personal reason) from the study, however, according to the protocol was included in the pharmacokinetic and statistical analysis.

- **Statistical methods**

Statistical analyses were performed on the pharmacokinetic parameters using the General Linear Models Procedure (PROC GLM) of SAS Software (version 9.4). The parameters: Tmax, Kel and t1/2 were analysed statistically using the non-transformed data. The natural log transformed parameters: ln-AUC0-t and ln-Cmax were also analysed.

Four minor protocol deviations consisting of PK sample collection time deviations of maximum 05 minutes due to difficulty in blood drawn and one protocol deviation consisting of housing deviation in period 2 (subject number 24 was withdrawn after 33.00 hours post dose in period-2 due to personal reason) have been reported during the study.

All concentration values below the lower limit of quantification (BLOQ) have been set to zero, concentration obtained as 0, <0. No Peak will be reported as Zero for all pharmacokinetic and statistical calculations. Any missing samples will be reported as 'M' and have not been included for pharmacokinetic and statistical analysis.

Individual and mean plasma concentration vs. time plots were generated on both linear and semi-log axis for pomalidomide.

The summary statistics (for relevant pharmacokinetic parameters) have been computed and reported for both test and reference products of pomalidomide.

The In-transformed pharmacokinetic parameters Cmax and AUC0-t of pomalidomide have been subject to analysis of variance (ANOVA).

ANOVA model included terms for sequence, formulation, period and subject (Sequence) as fixed effects. The sequence effect has been tested using the subject (Sequence) effect as an error term.

The period and treatment effects have been tested at 5% level of significance and sequence effects have been tested at 10% level of significance.

Two one-sided tests for bioequivalence and 90% confidence intervals for the ratio of least squares mean between drug formulations have been calculated, for In-transformed data of Cmax and AUC0-t of pomalidomide. The power of the test to detect 20% difference between test and reference products has been computed and reported for Pomalidomide.

Ratio of least squares means of test and reference products have been computed for ln-transformed pharmacokinetic parameters Cmax and AUC0-t of pomalidomide.

Ratio analysis have been reported for in-transformed pharmacokinetic parameters Cmax and AUC0-t of pomalidomide.

Intra-subject variability have been computed for In-transformed pharmacokinetic parameters Cmax and AUC0-t of pomalidomide.

*Criteria for conclusion of bioequivalence*

The acceptance criteria for bioequivalence were that the entire confidence intervals for the difference of means of Ln-transformed Cmax and AUC0-t should be within 80.00% -125.00%.

The pharmacokinetic parameters calculated are appropriate for a single dose bioequivalence study.

Standard bioequivalence criteria are proposed for the primary pharmacokinetic endpoints Cmax and AUC0-t which is adequate.

## Results

**Table 11: Pharmacokinetic parameters for pomalidomide (non-transformed values)**

| Pharmacokinetic parameter | Test | | Reference | |
|---|---|---|---|---|
| | **Arithmetic mean<br>geometric mean** | **SD<br>CV%** | **Arithmetic mean<br>geometric mean** | **SD<br>CV%** |
| $AUC_{(0-t)}$ (hr*ng/mL) | 543.026<br>530.923 | ±118.4064<br>21.8% | 534.483<br>521.857 | ±117.4873<br>22.0% |
| $AUC_{(0-\infty)}$ (hr*ng/mL) | 563.134<br>549.184 | ±130.5724<br>23.2% | 555.492<br>540.545 | ±131.6912<br>23.7% |
| $C_{max}$ (ng/mL) | 56.814<br>55.767 | ±11.3043<br>19.9% | 56.702<br>55.797 | ±9.9740<br>17.6% |
| $T_{max}$* (hr) | 2.000 | 0.670 – 5.000 | 2.000 | 0.670 – 4.000 |

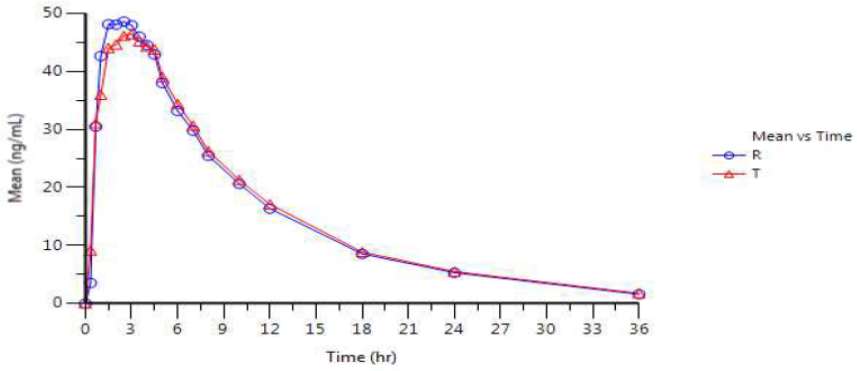
| | |
|---|---|
| $AUC_{0-t}$ | area under the plasma concentration-time curve from time zero to t hours |
| $AUC_{0-\infty}$ | area under the plasma concentration-time curve from time zero to infinity |
| $C_{max}$ | maximum plasma concentration |
| $T_{max}$ | time for maximum concentration (* median,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

**Table 12: Statistical analysis for pomalidomide (ln-transformed values)**

| Pharmacokinetic parameter | Geometric Mean Ratio Test/Reference | Confidence Intervals | CV%* |
|---|---|---|---|
| $AUC_{(0-t)}$ | 101.74 | 96.00 - 107.82 | 13.75% |
| $C_{max}$ | 99.95 | 93.16 - 107.22 | 16.68% |
| * estimated from the Residual Mean Squares | | | |

**Figure 3: Linear and semi log plot of mean pomalidomide plasma concentration**

**Linear Plot:**




**Semi Log Plot:**

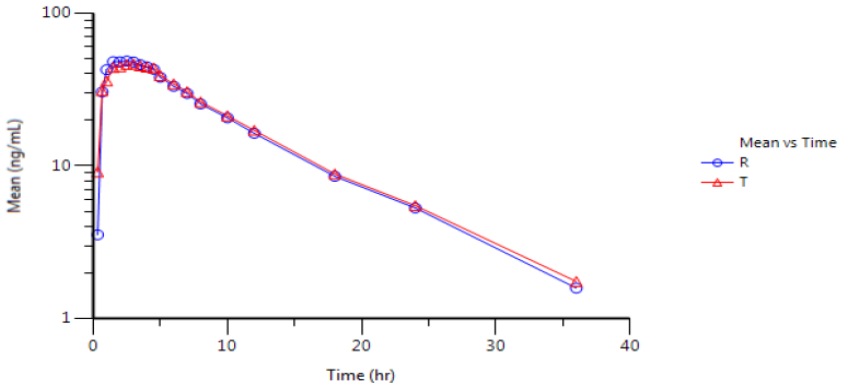



**Table 13: P-values from ANOVA table**

| Pharmacokinetic Parameters | p-value for Treatment/Formulation | p-value for period | p-value for Sequence |
|---|---|---|---|
| $AUC_{0-t}$ (hr.ng/mL) | 0.6183 | 0.8847 | 0.3912 |
| $C_{max}$ (ng/mL) | 0.9897 | 0.7885 | 0.0449 |

Source: Sub Section 16.2.6.2.1 of Section 16.2.6.2 of Appendix 16.2.6.

The pharmacokinetic parameter data including the confidence intervals and point estimates presented by the applicant are in line with the acceptance criteria of the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr – revised 2010).

Linear and semi-log plots have been submitted.

The 90% confidence intervals for the ln-transformed values for AUC0-t and Cmax were within the 80.00 – 125% limit and are considered acceptable.

Cmax was not observed in any subject at the first sample time point and pre-dose concentration has not been detected in any subject. The extrapolated AUC was not higher than 20% in any subject, and thus the blood sampling schedule up to 36 h was defined adequately.

The applicant does not report any statistically significant sequence, period or treatment effect for AUC0-t and does not report any statistically significant period or treatment effect for Cmax. However, a significant sequence effect was reported for Cmax.

The sequence effect in a bioequivalence study can indicate an unequal carryover effect. However, in the present study a true carryover effect is not visible as there are no pre-dose concentrations (> 5% of Cmax) in period-1, period-2 of any of the subjects. It is agreed with the applicant that the presence of sequence effect in a single dose study can be accepted if the following criteria are observed: the study involves only healthy volunteers, the drug is not an endogenous substance, An adequate washout period was established and the pre-dose samples do not show any detectable levels (> 5% of Cmax) of the drugs in all the volunteers and the study satisfies all the scientific and statistical criteria (for example protocol, validation, concentration data, statistical analysis, confidence interval).

- ***Safety data***

One (01) subject (subject no. 14) experienced 01 adverse event (during post study safety assessment) over the course of the study. The adverse event was mild in severity. No Serious Adverse Events (SAEs) were reported.

There were no clinically significant findings in the vital signs assessment or the laboratory tests in any of the subjects in the study.

Administrations of test and reference products to healthy subjects were safe and well tolerated.

### *2.4.2.2. Pharmacokinetic conclusion*

Based on the presented bioequivalence studies Pomalidomide 1 mg capsules is considered bioequivalent with Imnovid (Pomalidomide) 1 mg hard capsules and Pomalidomide 4 mg capsules is considered bioequivalent with Imnovid (Pomalidomide) 4 mg hard capsules, respectively.

The results of study POMA-CAZ-1004 with 4 mg formulation CAN be extrapolated to other strengths 2 mg and 3 mg, according to conditions in the *Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1*.

### *2.4.2.3. Pharmacodynamics*

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

## 2.4.3. Clinical efficacy

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

## 2.4.4. Clinical safety

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

## 2.4.5. Discussion on clinical aspects

To support the application, the company has submitted two bioequivalence studies, POMA-CAZ-1003 and POMA-CAZ-1004, and literature data on clinical pharmacology, efficacy, and safety, which is considered appropriate and relevant for a generic product application.

The studies were single oral dose, open labelled, randomised, two-period, two-treatment, two-sequence, cross over to demonstrate essential similarity between Pomalidomide Capsules 1 mg and Imnovid 1 mg hard capsules MAH Bristol-Myers Squibb Pharma EEIG and Pomalidomide Capsules 4 mg and Imnovid 4 mg hard capsules MAH Bristol-Myers Squibb Pharma EEIG in healthy, adult male human subjects under fasting conditions.

The applicant has stated that the study has been conducted in compliance with GCP and GLP requirements and during the assessment, no issue of GCP non-compliance arose.

The test product is an immediate release formulation. According to the SmPC of the reference product, the medicinal product can be taken with or without food. Thus bioequivalence single dose studies conducted under fasting conditions are acceptable. Pomalidomide exhibits linear, time-dependent pharmacokinetic over the therapeutic dose range. The two bioequivalence studies have been performed with the highest and the lowest strengths, i.e., 1 mg and 4 mg, respectively, due to the deviation from proportional composition, which is in line with the Guideline on the investigation of bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1.

Overall, the studies design is acceptable and in line with the pharmacokinetic properties of Pomalidomide.

The sampling period was sufficient, the sampling schedule and wash-out period were adequate considering the tmax and the t1/2. Since AUC0-t covers at least 80% of AUC0-∞, the sampling schedule covers the plasma concentration time curve long enough.

The population was chosen according to the guidelines. Bioanalytical method had satisfactory performance and was adequately validated. Another concern was raised in line with the ICH M10 guideline on bioanalytical method validation and study sample analysis, that came into effect on the 21 January 2023, thus, 100% of chromatograms have been requested to be submitted for bioequivalence studies.

The pharmacokinetic and statistical methods applied were appropriate for a single-dose study.

The 90% confidence intervals for ln-transformed pharmacokinetic variables Cmax and AUC0-t were within the conventional bioequivalence range of 80.00% to 125.00%.

Both formulations were well tolerated in the conducted bioequivalence studies.

Additionally, the applicant requested biowaiver for Pomalidomide Viatris 2 mg and 3 mg hard capsules. To support the request, a justification and results of comparative dissolution tests (0.1N hydrochloric

acid, pH 4.5 acetate buffer and pH 6.8 phosphate buffer) have been provided. The *in vitro* dissolution tests comparing the *in vitro* dissolution similarity between additional strengths and the test bio-batch of 4 mg over physiological pH range were conducted.

The dissolution methodology using the Ph. Eur. paddle apparatus was in accordance with the Guideline on the investigation of bioequivalence and no surfactant was used. The use of o helix sinker with different dimensions than the ones described in Ph.Eur was adequately justified.

The applicant's presentation of the biowaiver for 2 mg and 3 mg strengths is considered acceptable.

At pH medium 0.1 N HCl and 6.8 phosphate buffer, the applicant has not calculated the f2 similarity factor since more than 85% of the labelled amount of the drug was released within 15 minutes, based on average value for dissolution from 12 units, therefore, at these pH medium dissolution profiles can be accepted as similar, without further mathematical calculations.

At pH medium 4.5 acetate buffer, f2 was >50. For the f2 similarity evaluation only the first time points have been considered :10 min, 15 min and 20 min and the last sampling times have been ignored. This is correct because the last sampling time considered for f2 calculation should be the one when either of the products reaches 85% or more dissolved. Therefore, it is correct to exclude the later points where profiles are more similar since the plateau above 85% is being reached.

The similarity of the dissolution profiles of 2 mg, 3 mg and 4 mg strengths at pH medium 4.5 acetate buffer is considered demonstrated. Therefore, the provided dissolution data between the additional strengths and the biobatch can be accepted for the requested strength based biowaiver. *In vitro* dissolution tests comparing the *in vitro* dissolution similarity between the strengths of the test and the reference product tested in the bioequivalence studies over physiological pH range were conducted.

The results of the *in vitro* dissolution tests have shown that the similarity of the dissolution profiles between the test and the reference products at 1 mg strength used in the BE study cannot be confirmed using the f2 statistics at pH medium 4.5 acetate buffer and 6.8 phosphate buffer.

For the 4 mg strength the conditions for f2 calculation were not able to be fulfilled in either pH media.

The possible reasons for the differences in the dissolution profiles between the test and the reference products at 1 mg strength and 4 mg strength used in the conducted BE studies have been adequately discussed and justified based on the different qualitative composition, manufacturing process and attributes of API. The test product is being manufactured by dry granulation using a micronised API, considering that the active substance it is a BCS class IV. The clarification was deemed acceptable.

The bioequivalence between Pomalidomide 1 mg capsules and EU reference product Imnovid (Pomalidomide) 1 mg hard capsules and Pomalidomide 4 mg capsules and EU reference product Imnovid (Pomalidomide) 4 mg hard capsules under fasting conditions was demonstrated, according to the Guideline on the investigation of bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1 and *in vivo* data prevail.

## 2.4.6. Conclusions on clinical aspects

Based on the presented bioequivalence studies Pomalidomide Viatris 1 mg capsules is considered bioequivalent with Imnovid (Pomalidomide) 1 mg hard capsules and Pomalidomide Viatris 4 mg capsules is considered bioequivalent with Imnovid (Pomalidomide) 4 mg hard capsules, respectively.

The results of study POMA-CAZ-1004 with 4 mg formulation CAN be extrapolated to other strengths 2 mg and 3 mg, 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 14: Summary of safety concerns**

| | |
|---|---|
| Important Identified Risks | • Teratogenicity<br>• Severe infection due to neutropenia and pancytopenia<br>• Thrombocytopenia and bleeding<br>• Cardiac failure<br>• Non-melanoma skin cancer |
| Important Potential Risks | • Other second primary malignancies<br>• Cardiac arrhythmia |
| Missing Information | None |

### 2.5.2. Pharmacovigilance plan

**Table 15: Additional Pharmacovigilance Activities**

| **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 DLP of the PSUR |

### 2.5.3. Risk minimisation measures

**Table 16: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern**

| Safety Concern | Risk Minimisation Measures | Pharmacovigilance Activities |
|---|---|---|
| Teratogenicity | Routine risk minimisation measures:<br>SmPC Sections 4.3, 4.4, 4.6, 4.8 and 5.3<br>PL Section 2<br><br>Additional risk minimisation measures:<br>Pregnancy Prevention Programme (PPP): Educational Programme (Educational HCP's kit to include educational HCP brochure, educational brochures for patients, patient card, risk awareness forms, and information on where to find latest SmPC), Therapy Management, | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>- Expedited reporting of all pregnancies and abnormal pregnancy test results<br>- Optimise data collection and reporting of pregnancies by use of pregnancy report forms in HCP Kits<br>a- Follow-up of abnormal pregnancy test results |

| Safety Concern | Risk Minimisation Measures | Pharmacovigilance Activities |
|---|---|---|
| | System to ensure appropriate measures have been completed) | - Follow-up of all pregnancies until outcome is known.<br>- Follow-up of infant until one year after delivery<br>- Root cause analysis of failed MAH PPP as part of standard follow-up<br>- Review in PSURs (periodic and cumulative).<br><br>Additional pharmacovigilance activities: monitoring of<br>implementation and effectiveness<br>of the pregnancy prevention programme in routine PSURs |
| Severe infection due to neutropenia and pancytopenia | Routine risk minimisation measures:<br>SmPC Sections 4.2, 4.4 and 4.8<br>PL Sections 2 and 4<br><br>Additional risk minimisation measures:<br>None | Routine pharmacovigilance activities and targeted follow up questionnaire |
| Thrombocytopenia and bleeding | Routine risk minimisation measures:<br>SmPC Sections 4.2, 4.4 and 4.8<br>PL Sections 2 and 4<br>Additional risk minimisation measures:<br>Educational HCP brochure, Patient brochure | Routine pharmacovigilance activities and targeted follow up questionnaire |
| Cardiac Failure | Routine risk minimisation measures:<br>SmPC Sections 4.4 and 4.8<br>PL Sections 2 and 4<br><br>Additional risk minimisation measures:<br>Educational HCP brochure | Routine pharmacovigilance activities and targeted follow up questionnaire |

| Safety Concern | Risk Minimisation Measures | Pharmacovigilance Activities |
|---|---|---|
| Non-melanoma skin cancer | Routine risk minimisation measures:<br>SmPC Sections 4.4 and 4.8<br>PL Section 2 and 4<br><br>Additional risk minimisation measures:<br>None | Routine pharmacovigilance activities and targeted follow up questionnaire |
| Other second primary malignancies | Routine risk minimisation measures:<br>SmPC Section 4.4<br>PL Section 2<br><br>Additional risk minimisation measures:<br>None | Routine pharmacovigilance activities and targeted follow up questionnaire |
| Cardiac arrhythmia | Routine risk minimisation measures:<br>SmPC Section 4.8<br>PL Section 4<br><br>Additional risk minimisation measures:<br>None | Routine pharmacovigilance activities and targeted follow up questionnaire |

### 2.5.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 1.0 is 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 Duloxetine Mylan 30 mg hard gastro-resistant capsules (PIL B) and to Imnovid 1 mg, 2mg, 3mg, 4mg hard capsules. 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 1 mg, 2 mg, 3 mg, 4 mg capsule, hard is indicated in combination with bortezomib and dexamethasone 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 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 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 nor on the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The bioequivalence study forms the pivotal basis with a single oral dose, open labelled, randomised, two-period, two-treatment, two-sequence, cross over study in normal, healthy, adult male human subjects under fasting conditions investigating the bioequivalence of Pomalidomide 1 mg hard capsules to Celgene Europe B.V. of Imnovid (Pomalidomide) 1 mg Hard Capsules and Pomalidomide 4 mg hard capsules to Celgene Europe B.V. of Imnovid (Pomalidomide) 4 mg Hard Capsules, respectively. 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 Pomalidomide 1 mg hard capsules and Pomalidomide 4 mg hard capsules, respectively met the protocol-defined criteria for bioequivalence when compared with the [reference product]. The point estimates and their 90% confidence intervals for the parameters AUC0-t, AUC0-∞, and Cmax were all contained within the protocol-defined acceptance range of [range, e.g. 80.00 to 125.00%]. Bioequivalence of the two formulations was demonstrated.

The requested biowaiver for the additional strengths 2 mg and 3 mg strengths is acceptable.

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.

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

# 4. Recommendations

***Similarity with authorised orphan medicinal products***

The CHMP by consensus is of the opinion that Pomalidomide Viatris 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. It is considered that Pomalidomide Viatris is similar to Imnovid (Pomalidomide) within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. However Imnovid was withdrawn from the Community register of orphan medicinal products in August 2023 at the end of the 10-year period of market exclusivity. Of note the filing of the application was accepted prior to the expiry of market exclusivity based on the reference product's MAH limited waiver of orphan data exclusivity in favour of Viatris in line with the applicable derogation.

***Derogation from market exclusivity***

The CHMP by consensus is of the opinion that pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000 the following derogation laid down in Article 8.3 of Regulation (EC) No. 141/2000 applies:

- the holder of the marketing authorisation for Imnovid has given their consent to the applicant to submit the application before the orphan designation expired.

***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 Viatris is favourable in the following indications:

> Pomalidomide Viatris 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 Viatris 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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

***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 are provided with an Educational Healthcare Professional's Kit containing the following:
     - Educational Healthcare Professional Brochure
     - Educational brochures for patients
     - Patient cards
     - Risk awareness forms
     - Information where to find the latest Summary of Product Characteristics (SmPC)
- 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 marketing of the product.
- 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
- The MAH should agree on the implementation of the controlled access programme 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:

**Educational Healthcare Professional brochure**

- Brief background on pomalidomide
- Maximum duration of prescription
  - 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 Viatris for healthcare professionals and caregivers
- Obligations of the health care professional who intend to prescribe or dispense pomalidomide

- 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
- 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 Viatris

- 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 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 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 pomalidomide treatment
    - For one week following final dose
  - That he should not donate semen or sperm during therapy (including during dose interruptions) and for 7 days after discontinuation of pomalidomide treatment
  - That if his partner becomes pregnant whilst he is taking pomalidomide or shortly after he has stopped taking pomalidomide he should inform his treating doctor immediately

- Requirements in the event of pregnancy
  - Instructions to stop pomalidomide immediately upon suspicion of pregnancy if female patients

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

All patient brochures 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 for patients, caregivers and family members
- National or other applicable specific arrangements for a prescription for pomalidomide to be dispensed
- That the patient must not give pomalidomide to any other person
- That the patient should not donate blood during therapy (including during dose interruptions) and for 7 days after discontinuation of pomalidomide 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
- 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 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 has no contraception (even if man has had vasectomy)
  - During pomalidomide treatment (including dose interruptions)
  - For 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 for 7 days after discontinuation of pomalidomide 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 Viatris
    - the physician prescribing Pomalidomide Viatris 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 Viatris 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 Viatris
  - 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 Viatris

- 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 Viatris
  - 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 are provided with an Educational Healthcare Professional's Kit containing the following:
     - Educational Healthcare Professional brochure
     - Educational brochures for patients
     - Patient cards
     - Risk awareness form
     - Information on where to find latest Summary of Product Characteristics (SmPC)
   - 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 marketing of the product.
   - 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
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- Guidance on handling the blister or capsule of Pomalidomide Viatris for healthcare professionals and caregivers
- Obligations of the health care professional who intend to prescribe or dispense pomalidomide
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  - 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 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 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 pomalidomide treatment
    - For one week following final dose
  - That he should not donate semen or sperm during therapy (including during dose interruptions) and for 7 days after discontinuation of pomalidomide treatment
  - That if his partner becomes pregnant whilst he is taking pomalidomide or shortly after he has stopped taking pomalidomide he should inform his treating doctor immediately

- Requirements in the event of pregnancy
  - Instructions to stop pomalidomide immediately upon suspicion of pregnancy if female patients
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- 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

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  - 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 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 has no contraception (even if man has had vasectomy)
  - During pomalidomide treatment (including dose interruptions)
  - For 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 for 7 days after discontinuation of pomalidomide treatment

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- 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 Viatris
    - the physician prescribing Pomalidomide Viatris 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 Viatris 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 Viatris
  - 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 Viatris
  - 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 Viatris
  - 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.