19 September 2024
EMA/518385/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Pomalidomide Teva

International non-proprietary name: Pomalidomide

Procedure No. EMEA/H/C/006302/0000

Note

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

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List of abbreviations

ANC	Absolute nucleated cell count
ASMF	Active Substance Master File = Drug Master File
AUC	Area Under the Curve
BCS	Biopharmaceutics Classification System
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CFU	Colony Forming Units
CHMP	Committee for Medicinal Products for Human use
CI	Confidence interval
CL/F	Apparent clearance
Cmax	Maximum plasma concentration
CR	Complete response
DDB1	Damage-binding protein 1
DEX	Dexamethasone
DLT	Dose-limiting toxicity
DSC	Differential Scanning Calorimetry
DVS	Dynamic Vapour Sorption
EMA	European Medicines Agency
GC	Gas Chromatography
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IR	Infrared
IV	Intravenous
KF	Karl Fischer titration
LEN	Lenalidomide
MM	Multiple myeloma
MO	Major Objection
MS	Mass Spectrometry
NLT	Not less than
NMR	Nuclear Magnetic Resonance
NMT	Not more than
OR	Odds ratio

PCTFE	Polychlorotrifluoroethylene
PD	Progressive disease
PDA	Photodiode Array Detector
PE	Polyethylene
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetics
POM	Pomalidomide
PT	Preferred term
PVC	Polyvinyl chloride
QbD	Quality by design
Q/F	Distribution clearance
QD	Once daily
QTPP	Quality target product profile
SmPC	Summary of Product Characteristics
SOC	System organ class
TAMC	Total Aerobic Microbial Count
TGA	Thermo-Gravimetric Analysis
Tmax	Time for a drug to reach the maximum concentration (Cmax)
TSE	Transmissible Spongiform Encephalopathy
TYMC	Total Combined Yeasts/Moulds Count
ULN	Upper limits of normal
UV	Ultraviolet
VC/F	Apparent volume of the central compartment
XR(P)D	X-Ray (Powder) Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Teva GmbH submitted on 11 September 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Pomalidomide Teva, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 23 February 2023.

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

The applicant applied for the following indication:

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

1.2. Legal basis, dossier content

The legal basis for this application refers to:

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

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Imnovid instead of non-clinical and clinical unless justified otherwise.

The chosen reference product is:

- Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA: Product name, strength, pharmaceutical form: Imnovid, 1mg, 2mg, 3mg, 4mg, capsules hard
- Marketing authorisation holder: Bristol-Myers Squibb Pharma EEIG
- Date of authorisation: 05-08-2013
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number:
- 1mg - EU/1/13/850/001; 005
- 2mg - EU/1/13/850/002; 006
- 3mg - EU/1/13/850/003; 007

- 4mg - EU/1/13/850/004; 008

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

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

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

- Product name, strength, pharmaceutical form: Imnovid, 4mg, capsules hard
- Marketing authorisation holder: Bristol-Myers Squibb Pharma EEIG
- Date of authorisation: 05-08-2013
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number(s): EU/1/13/850/004; 008
- Bioavailability study number(s): Study code: BE-2181-22

1.3. Information relating to orphan market exclusivity

1.3.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.4. Scientific advice

The applicant did not seek scientific advice from the CHMP.

1.5. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Ewa Balkowiec Iskra

The application was received by the EMA on	11 September 2023
The procedure started on	28 September 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	11 December 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	3 January 2024
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	25 January 2024
The applicant submitted the responses to the CHMP consolidated List of Questions on	24 May 2024
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	27 June 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 July 2024
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	25 July 2024
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	20 August 2024
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	2 September 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Pomalidomide Teva on	19 September 2024
The CHMP adopted a report on similarity of Pomalidomide Teva 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).	19 September 2024

2. Scientific discussion

2.1. Introduction

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

The applicant has developed Pomalidomide Teva 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 Teva 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 Teva 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 and 4 mg of pomalidomide as active substance.

Other ingredients are: capsule contents (lactose monohydrate, crospovidone, povidone, sodium laurilsulfate, sodium stearyl fumarate); capsule shell (gelatin, titanium dioxide (E171), iron oxide yellow (E172) (for 1 mg, 2 mg and 3 mg capsule strengths), brilliant blue FCF (E133), and iron oxide red (E 172) (for 2 mg capsules only); printing ink (shellac (E904), iron oxide black (E172), potassium hydroxide (E525), propylene glycol (E1520) and concentrated ammonia solution.

The product is available in PVC/PE/PVDC-Aluminium or PVC/PCTFE/PVC-Aluminium blisters as described in section 6.5 of the SmPC.

2.2.2. Active substance

2.2.2.1. General Information

The chemical name of pomalidomide is (*RS*)-4-Amino-2-(2,6-dioxo-piperidin-3-yl)-isoindoline-1,3-dione corresponding to the molecular formula $C_{13}H_{11}N_3O_4$. It has a relative molecular mass of 273.24 g/mol and the following structure:

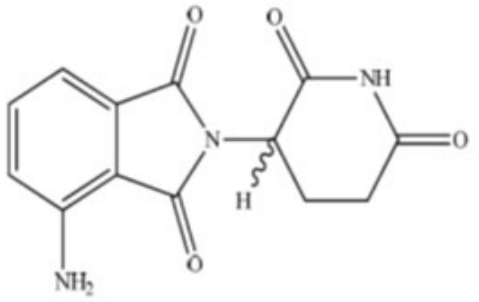

Figure 1. Active substance structure

The chemical structure of pomalidomide was elucidated by a combination of CHN analysis, FT-IR spectroscopy, proton Nuclear Magnetic Resonance (NMR), carbon Nuclear Magnetic Resonance and Mass spectroscopic (MS) studies, thermal analysis (DSC), TGA analysis, DVS analysis and UV spectroscopy.

The active substance is a non-hygroscopic pale yellow to yellow colour powder, soluble in dimethyl sulphoxide and practically insoluble in water.

Pomalidomide exhibits stereoisomerism due to the presence of one chiral centre. Enantiomeric purity is controlled routinely by specific optical rotation.

Polymorphism has been observed for active substance. Based on the X-ray powder diffraction studies it is concluded that the polymorph produced by the active substance manufacturer is the intended form . The other polymorphic forms are not relevant to the applied finished product given the active substance manufacturing conditions

There is no monograph of pomalidomide in the European Pharmacopoeia.

2.2.2.2. 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.

Pomalidomide is synthesised in four main steps using well defined active substance starting materials. In the initial submission the ASMF holder proposed a 3- stage synthesis using other starting materials. This was not considered acceptable and two major objections (MO) were raised by the CHMP. To address this concern the ASMF holder redefined the starting materials This is considered acceptable

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

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

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

The active substance is packaged in bags that are kept in a sealed HDPE container. Primary packaging complies with which complies with Commission Regulation (EU) 10/2011, as amended.

2.2.2.3. Specification

The active substance specification includes tests for description (visual), solubility (Ph. Eur.), identification (IR, HPLC), water content (Coulometry), optical rotation (Ph. Eur.), sulphated ash (Ph. Eur.), related substances (HPLC), assay (HPLC), residual solvents (GC), particle size distribution (laser diffraction) and identification of crystalline form (XRPD).

The in-house specification was developed and based on development, results obtained during the validation study, compendial general tests and ICH requirements: ICH Q6A, ICH Q3A and ICH Q3C. The proposed specification is suitable to control the pharmaceutical quality of the active substance by the manufacturer and is acceptable.

The maximum daily dose (MDD) for pomalidomide is 4 mg/day. Therefore, the ICH required thresholds for reporting, identification and qualification in the active substance are 0.05%, 0.10% and 0.15%, respectively. The proposed acceptance criteria for relevant impurities are in accordance with these thresholds. Some specified impurities contain structural alerts for mutagenicity and are controlled in accordance with ICH M7.

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

Batch analysis data from the ASMF holder of pomalidomide have been presented. The results are in line with the proposed specification are consistent from batch to batch. In addition, certificates of analysis from the finished product manufacturer are presented. The results comply with the proposed specification.

2.2.2.4. Stability

Stability data from production scale batches of active substance stored in the intended commercial package for up to 72 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested*:* description, identification (IR, HPLC), water content, optical rotation, related substances, assay and polymorphic identity. The analytical methods used were the same as for release and were stability indicating.

All tested parameters were within the specifications under long term and accelerated conditions.

Results on stress conditions under heat, humidity, sunlight, photolytic, water, acid, base and oxidation stress conditions were also provided. The active substance is slightly sensitive under extreme acidic conditions, oxidation and water hydrolysis. The active substance is very sensitive to alkaline conditions. Pomalidomide is stable to heat sunlight, UV direct, LUX direct, UV indirect and LUX indirect.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 60 months with no special storage conditions is acceptable.

2.2.3. Finished medicinal product

2.2.3.1. Description of the product and pharmaceutical development

The finished product Pomalidomide Teva consists of hard gelatin capsules containing 1, 2, 3 or 4 mg of pomalidomide, packaged in PVC/PE/PVDC-Aluminium or PVC/PCTFE/PVC-aluminium blisters in various pack sizes.

The different capsule strengths differentiate in the capsule size (size 4 – strength 1 mg, size 2- strengths 2, 3, 4 mg) and/or the colour and imprinting of the body of the capsule as follows:

Pomalidomide 1 mg Hard Capsules:

Hard gelatin capsule No. 4 (overall closed length approximately 14.3 mm) with Blue opaque cap and Yellow opaque body, filled with yellow to light yellow powder, Imprinting "T" on the cap and "1" on the body.

Pomalidomide 2 mg Hard Capsules:

Hard gelatin capsule No. 2 (overall closed length approximately 18.0 mm) with Blue opaque cap and Orange opaque body, filled with yellow to light yellow powder, Imprinting "T" on the cap and "2" on the body.

Pomalidomide 3 mg Hard Capsules:

Hard gelatin capsule No. 2 with Blue opaque cap and Green opaque body, filled with yellow to light yellow powder, Imprinting "T" on the cap and "3" on the body.

Pomalidomide 4 mg Hard Capsules:

Hard gelatin capsule No. 2 with Blue opaque cap and Light Blue opaque body, filled with yellow to light yellow powder, Imprinting "T" on the cap and "4" on the body.

The finished product has been developed to be a generic equivalent to the reference medicinal product Imnovid capsules. Consequently, the objective was to prepare a pharmaceutical form being essentially similar to it. Both, the proposed generic and EU reference product use gelatin hard capsules. However, the generic medicinal product differs from the reference medicinal product in the excipients. The filler in the generic product is lactose monohydrate (instead of mannitol used in Imnovid), and crospovidone (disintegrant) and sodium laurilsulfate (surfactant) have been added to the generic formulation. The changes are due to the difference in manufacturing technology, which is wet granulation for the generic product, while the EU reference product is reported to use dry mix. The wet granulation process was selected due to low percentage of pomalidomide, to achieve homogenous uniformity of blend and content.

All components of the proposed dosage form (quantitative and qualitative content of capsule, ingredients of capsule shell, composition of the imprinting) as intended for marketing, have been clearly stated. Function and reference to quality standards (in house specification, monograph in Ph. Eur. or Commission Regulation (EU) No 231/2012) have been specified. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel

excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

Compatibility studies between the active substance and each of the excipients were conducted in order to identify any potential interactions between the active substance and the chosen excipients. All results were within the specification and supported their selection. A Quality by Design (QbD) approach was used to develop these generic pomalidomide capsules to be therapeutically equivalent to the EU reference product. However, a design space was not claimed by the applicant.

The Quality target product profile (QTPP) was defined based on the active substance properties, EU reference product characterisation, and consideration of the EU reference product labelling and intended patient population.

The QTPP was to develop immediate release hard capsules for oral administration containing 1, 2, 3, and 4 mg of pomalidomide as generic of Imnovid with the same dosage form, route of administration and strengths. The product was demonstrated to bioequivalent to the reference product. The manufacturing process, formulation and container closure systems were selected to support the stability of the product and its quality attributes such as description, identification, assay, uniformity of dosage units, degradation products, dissolution, and water content.

Critical quality attributes (CQAs) were identified based on the potential severity of harm to a patient (safety and efficacy) resulting from failure to meet that quality attribute of the drug product. These included: capsule size, assay, uniformity of dosage units, degradation products, dissolution and residual solvent content. The pharmaceutical development focused on the CQAs that could be affected by a realistic change to the finished product formulation or manufacturing process. These included: assay, content uniformity, degradation products/impurities and dissolution.

The formulation and manufacturing development have been evaluated through the use of risk assessment to identify the critical product quality attributes and critical process parameters. A risk analysis was performed in order to define critical process steps and process parameters that may have an influence on the finished product quality attributes. The risk identification was based on the prior knowledge as well as on the experience from formulation development, process design and scale-up studies.

Pomalidomide is practically insoluble over the physiological pH range and not pHs dependent. Pomalidomide is a drug with low solubility and low permeability, making it a biopharmaceutical classification system (BCS) class IV drug

The choice of the dissolution method has been adequately justified. The discriminatory power of the dissolution method has been demonstrated.

Comparative dissolution profiles of the generic bio-batch (4 mg) *vs.* the reference product bio-batch across the physiological pH range of 1.2, 4.5 and 6.8 have been presented. Similarity was observed in all cases (f2>50).

Pomalidomide Teva capsules, hard formulation application comprises also of remaining 1 mg, 2 mg and 3 mg strengths which were not tested in the bioequivalence studies. Since pharmacokinetics of pomalidomide is linear the highest, 4 mg strength was identified as the most sensitive strength to detect a potential difference between the test and the reference medicinal product and for the additional strengths A proportionality based biowaiver has been proposed in compliance with general biowaiver criteria (ref. Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**)).

Comparative dissolution profiles of the generic bio batch (4mg strength-) vs. the 1, 2 and 3 mg strengths at pH 1.2, 4.5 and 6.8 were also presented.

In order to demonstrate the similarity between the strengths, the applicant performed dissolution tests at pH 1.2, 4.5 and 6.8 as requested by CHMP. Teva's pomalidomide capsules were rapidly dissolved (≥ 85% of the drug was dissolved within 15 minutes) at pH 4.5 and 0.1N HCl. Thus, the dissolution profiles are considered similar without further mathematical evaluation. Similarity at pH 6.8 was also confirmed.

The manufacturing process development has been adequately described, including holding time stud which support the storage of pomalidomide blend.

The primary packaging consists of PVC/PE/PVDC-aluminium or PVC/ACLAR/PVC-aluminium blister are described as stated in the SmPC. 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.

2.2.3.2. Manufacture of the product and process controls

The manufacturing process consists of 7 main steps: premixing, granulation, drying, milling, final mixing, encapsulating, packaging. The critical steps in the manufacture of the finished product are granulation, mixing and encapsulation. The process is considered to be a non-standard manufacturing process given the low drug content in the formulation (≤2% of composition).

A flow diagram of manufacturing process and its narrative description have been presented with sequence of excipients addition, type of equipment, some process parameters, indication of the critical steps.

The first day of production will be taken as the start of the shelf life in line with the CHMP Note for Guidance on Start of Shelf-life of the Finished Product Dosage Form (CPMP/QWP/072/96).

A final blend holding time has been proposed, which is supported by development studies (see pharmaceutical development section).

Bulk holding time is supported by a bulk stability (see stability section below).

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

2.2.3.3. Product specification(s)

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form: appearance (visual), uniformity of dosage units (Ph. Eur.), identification of pomalidomide (HPLC, PDA), degradation products (HPLC), assay (HPLC), dissolution (HPLC), residual solvent content (GC), loss on drying (Ph. Eur.), identification test for colouring agents (chemical reaction, colour reaction, HPLC), microbiological examination of non-sterile products (TAMC, TYMC, *E. coli*) (Ph. Eur.).

Some of pomalidomide hard capsules impurities bear structural alerts for mutagenicity, and therefore, are categorised as class 3 impurities. Limits according to ICHQ3A/B are justified based on ICH S9 and not ICH M7 given the advanced cancer indication.

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

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 in the finished product specification. The information on the control of elemental impurities is satisfactory.

Following a request from the CHMP a risk assessment concerning the potential presence of nitrosamine impurities in the finished product considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020) was provided. Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary

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

Batch analysis results are provided for three production batches of each strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.2.3.4. Stability of the product

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

Samples were tested for appearance, assay, related substances, dissolution, loss on drying and microbiological quality. The analytical methods used were the same as for release and were stability indicating.

No significant changes have been observed, all parameters remained within the shelf-life specification limits under long term and accelerate conditions.

In accordance with EU GMP guidelines[1], any confirmed out-of-specification result, or significant negative trend observed during the ongoing stability program, should be reported to the Rapporteur and EMA.

In addition, one batch of each product strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The obtained results complied with the proposed specifications. Therefore, the finished product is considered to be photostable.

Stability studies at 25°C / 60% RH condition have been performed on three bulk product production scale batches from each strength packaged in the proposed container for bulk storage. The results

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complied with the specifications and support the proposed holding time and storage condition in the proposed container.

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

Confirmation that the shelf-life of the finished product is calculated in accordance with the Note for Guidance on Start of Shelf-life of the Finished Dosage Form (CPMP/QWP/072/96) is provided.

2.2.3.5. Post approval change management protocol

n/a

2.2.3.6. Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

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

2.2.4. Discussion on chemical, and pharmaceutical aspects

The finished product is a generic of Imnovid hard gelatin capsules.

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner.

During evaluation, two major objections were raised by the CHMP in relation to the originally proposed active substance starting materials. The responses from the applicant to the MOs were considered satisfactory and all the issues were considered to be resolved.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.2.6. Recommendations for future quality development

n/a

2.3. Non-clinical aspects

2.3.1. Introduction

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

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

2.3.2. Ecotoxicity/environmental risk assessment

No environmental risk assessment (ERA) studies were submitted. This was justified by the applicant as the introduction of Pomalidomide Teva is considered unlikely to result in any significant increase in the combined sales volumes for all pomalidomide containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar.

2.3.3. Discussion on non-clinical aspects

The non-clinical overview provided by the applicant is considered comprehensive and sufficient to support the pomalidomide Teva Marketing authorisation application. The non-clinical sections of the SPC are in line 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 considered acceptable.

The ERA submitted by the applicant is acceptable.

2.3.4. Conclusion on the non-clinical aspects

There are no objections to the approval of Pomalidomide Teva 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 one bioequivalence study with a cross-over design under fasting conditions. This study was the pivotal study for this application.

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 is of particular relevance.

GCP aspect

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

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

Exemption

A strength biowaiver was requested for Pomalidomide Teva 1 mg, 2 mg and 3 mg hard capsules.

All strengths are manufactured by the same manufacturing process and the qualitative composition of the different strengths is the same. Furthermore, the quantitative composition of the higher strength (4 mg) and the lower strengths (1 mg, 2 mg and 3 mg) is dose proportional.

In support of this biowaiver the applicant performed *in vitro* dissolution studies at three different buffers (0.1M Hydrochloric acid, Acetate buffer solution pH 4.5 and Phosphate buffer solution pH 6.8), with the test product that was used in the pivotal bioequivalence study (BEQ batch 4mg) and additional strengths of 1mg, 2mg and 3 mg of the test product. Dissolution tests were conducted under standard dissolution conditions with paddle apparatus (rotation speed of 50 rpm).

The dissolution results of 4 mg at pH 6.8 were similar to those of the 1, 2 and 3 mg strengths. At pH 4.5 similarity was demonstrated between 4 mg and 1 mg (data not shown). For the comparisons of the 2 and 3 mg at pH 4.5 and the 1, 2 and 3 mg in 0.1N HCl, although the dissolution profiles of all strengths demonstrated similar behaviour, f2 calculation could not be performed according to the requirements of the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1 – January. 2010). The dissolution values were slightly over 85% at 15 minutes interval (either 86% or 87% for some of the strengths), whereas the bio batch value was less than 85% at 15 minutes.

In order to provide further assurance for the similarity of the strengths, a comparison of the strengths was conducted using multiple capsules: 4 capsules 1 mg or 2 capsules 2 mg compared to 1 capsule 4 mg. The dissolution results and F2 calculations are provided below:

		Collection Times (minutes or hours)					f2
Dissolution Medium		10	15	20	30	45	
4* Pomalidomide 1mg Capsules 12 units Batch 2000064219	0.1N HCl-QC	68	76	81	87	91	69
2* Pomalidomide 2mg Capsules 12 units Batch 2000069270	0.1N HCl-QC	70	83	90	94	96	66
	pH 4.5	69	80	84	88	91	67
1* Pomalidomide 4mg Capsules 12 units Batch 2000063291	0.1N HCl-QC	64	79	86	92	94	
	pH 4.5	62	79	87	92	94	

The 3 mg strength dissolution test was carried out using 4 capsules and was compared to 3 capsules of the 4 mg strength. The dissolution results and F2 calculations are provided below:

Dissolution Medium		Collection Times (minutes or hours)					f2
		10	15	20	30	45	
4* Pomalidomide 3mg Capsules 12 units Batch 2000067714	0.1N HCl-QC	62	71	76	82	86	78
	pH 4.5	62	72	77	81	85	77
3* Pomalidomide 4mg Capsules 12 units Batch 2000063291	0.1N HCl-QC	59	68	73	80	85	
	pH 4.5	58	69	74	80	84	

Tabular overview of clinical studies

In support of this application, the applicant submitted one bioequivalence study (BE-2181-22).

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the study	Study Design and Type of control	Study Product(s); Dosage Regimen Route of Administration	Number of Subjects	Healthy subjects or Diagnosis of patients	Duration of Treatment	Study status; Type of Report
BA	Not Applicable								
BE	BE-2181-22	Module 5.3.1.2/comparative-ba-and-bioequivalence-study-reports/ report - body.pdf	The primary objective of the study was to assess the bioequivalence of Pomalidomide 4 mg Capsules, compared to that of Imnovid (Pomalidomide) 4 mg hard capsules following a single oral dose (1 × 4 mg capsule of test and reference product) in healthy human, adult male subjects when administered under fasting conditions. The secondary objective of the study was to assess the safety and tolerability of the test product and reference product in healthy human, adult male subjects.	This was an open label, randomized, single dose, two treatment, two period, two sequence, crossover bioequivalence study under fasting conditions	**Test Product (T)** Pomalidomide 4mg Capsules EU Batch No.: 2000063291 Per Oral **Reference Product (R)** Imnovid (Pomalidomide) 4 mg hard capsules Lot No. C2398AA Per Oral	Planned: 40+02 Enrolled: 40+02* Dosed in Period 01: 40 Period 02: 36 Completed : 36 Analyzed : 36 36# subjects completed both periods of the study and considered for pharmacokinetics and statistical analysis Withdrawn: 02 (Subject nos. 1004 and 1040) Dropped out: 02 (Subject nos. 1005, and 1012).	Healthy subjects	Single dose	Complete; ICH E3 Guideline (Structure and Content of Clinical Study Reports)

In addition, an abbreviated clinical study report for a single dose crossover comparative bioavailability pilot study (TVI-P8-456) was also submitted.

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

Study BE-2181-22: An open label, randomised, single dose, two-way crossover, bioequivalence study of Pomalidomide 4 mg Capsules in healthy human, adult male subjects under fasting conditions.

Methods

- **Study design**

This was an open label, randomised, single dose, two-treatment, two-period, two-sequence, crossover bioequivalence study under fasting conditions with a washout period of 7 days between treatments.

The primary objective of the study was to assess the bioequivalence of Pomalidomide 4 mg Capsules, compared to that of Imnovid (pomalidomide) 4 mg hard capsules following a single oral dose (1 × 4 mg capsule of test and reference product) in healthy human, adult male subjects when administered under fasting conditions.

The secondary objective of the study was to assess the safety and tolerability of the test product and reference product in healthy human, adult male subjects.

Study Initiation Date: 22 May 2023.

Study Completion Date (Period 02 check-out): 01 June 2023.

- **Test and reference products**

Both the reference and the test products are identical with regards to the strength and formulation intended to be marketed. The information regarding test and reference product is summarised in the Table below.

	Test Product	Reference Product
	T	R
Product	Pomalidomide 4mg Capsules EU	Imnovid (Pomalidomide) 4 mg hard capsules
Manufacturer/MAH	Teva Pharmaceutical Industries Ltd.18 Eli Hunvitaz st.kfar-saba 4410202 Israel	Celgene Distribution B.V Winthonloan 6N,3526 KV Utrecut Niederlaude
Distributed By	N/AP	N/AV
Description*	Hard gelatin capsule with blue opaque cap and light blue opaque body, filled with yellow to light yellow powder, imprinting "T" on the cap "4" on the body	Dark blue opaque cap and blue opaque body, with "POML 4mg" written on them.
Batch No.	2000063291	N/AP
Lot No.	N/AP	C2398AA
Manufacturing Date	December 19,2022	N/AV
Expiry Date	Until JUN 16,2023	06/2024
Retest Date	N/AP	N/AP

- **Population(s) studied**

Healthy adult male subjects aged 18 to 45 years (both inclusive), having a body mass index (BMI) between 18.5 kg/m2 to 30.0 kg/m2 (both inclusive), and weighing at least 50 kg, without evidence of underlying disease or clinically significant abnormal laboratory values at screening and who voluntarily consented to participate in the study were considered eligible to the Study.

- **Analytical methods**

Validation Of High Performance Liquid Chromatography Mass Spectrometric Method for measurement of Pomalidomide in human plasma using Pomalidomide D4 as an Internal Standard - Validation Protocol No. VP-637-23-01. The achiral analytical method was employed for this study. The isomers of pomalidomide occur in blood in proportions of 50/50%. It was also demonstrated that the rapid isomeric interconversion of pomalidomide isomers, compared to the relatively slower elimination rate constant, results in comparable exposure to R- and S-enantiomers (Li et al. 2014). Therefore, in humans, rapid isomeric interconversion of pomalidomide isomers results in comparable exposure to R- and S-enantiomers regardless of whether pomalidomide is administered as a single enantiomer or as a racemate. Consequently, it was possible to use an achiral method.

The analysis of pomalidomide was validated in the linear ranges of the analyte from 0.502 to 120.466 ng/mL.

The selectivity of the method was evaluated for six normal, one lipemic (triglyceride level >300 mg/dL) and one haemolysed (2% haemolysis) plasma lots. The accuracy of LLOQ samples prepared in haemolysed and lipemic plasma lots was 116.82% and 96.82%, respectively, which is within the acceptance criteria (80% to 120%). There was no interference found from haemolysed and lipemic blank plasma lots at mass transition and retention time of Pomalidomide and Pomalidomide D4 (I.S.).

Total of 1975 human plasma samples were analysed for pomalidomide concentrations using liquid chromatographic tandem mass spectrometric method. The samples storage conditions – time and temperature cover validated conditions. The %CV for calibration standards and QC samples were acceptable. The Time 0 levels were below the LLOQ for all patients and periods. The LLOQ was well established, with values not exceeding 5% of Cmax for all patients.

Incurred sample reproducibility was assessed for 152 samples (7.7%), and the results were acceptable, as the relative differences in repeated samples did not exceed 20% compared to the initial evaluation for 99.34% of reanalysed samples.

- **Pharmacokinetic variables**

The following pharmacokinetic parameters for pomalidomide plasma concentration was calculated using standard non-compartmental methods:

AUC0-t - The area under the plasma concentration versus time curve, from time 0 to the last measurable concentration, as calculated by the linear up/log down trapezoidal method.

AUC0-inf - The area under the plasma concentration versus time curve from time 0 to infinity. AUC0-inf is calculated as the sum of the AUC0-t plus the ratio of the last measurable plasma concentration to the elimination rate constant.

AUCratio - The ratio of AUC0-t to AUC0-inf.

Cmax - Maximum measured plasma concentration over the time span specified.

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

Kel - Apparent first-order terminal rate constant calculated from a semilog plot of the plasma concentration versus time curve. The parameter was calculated by linear least-squares regression analysis in the terminal log-linear phase (three or more non-zero plasma concentrations).

t½ - The apparent first-order terminal half-life was calculated as 0.693/Kel.

Residual area Extrapolated area (AUC(0-inf) - AUC(0-t))/ AUC(0-inf).

- **Statistical methods**

Analyses of variance (ANOVA) were performed on the log-transformed pharmacokinetic parameters AUC0-t, AUC0-inf and Cmax of Pomalidomide. The ANOVA model includes sequence, subjects nested within sequence, period and treatment as the fixed effects. All the fixed effects were tested at 5 % level of significance, using the residual error (mean square error or MSE) from the ANOVA as the error term. The sequence effect was also tested at the 10 % level of significance using the mean sum of square of subjects nested within sequence, from the ANOVA as the error term.

Each analysis of variance includes calculations of least-squares means (LSM), the difference between adjusted formulation means and the standard error associated with this difference.

Determination of sample size

The sample size calculation for this study was based on the intra-subject coefficient of variation (CV %) for Pomalidomide as obtained from sponsor study data.

Based on that the intra-subject CV % for Cmax was expected to be ~ 18 %. Thus, with the expected coefficients of variation for Cmax and assuming the true ratio falling within 91 % to 109.9%, the study had at least 34 evaluable subjects to show the bioequivalence with a power of 90 % at 5 % level of significance for a two-treatment, two-period, two sequence, crossover, bioequivalence study design using the bioequivalence limits (i.e. 80.00 % to 125.00 %).

Further, expecting certain dropouts and/ or withdrawals in the study, 06 additional subjects were planned to be included in the study. Thus, a total of 40 subjects were sufficient for this two-treatment, two-period, two-sequence, crossover, bioequivalence study for establishing the bioequivalence of the test to the reference drug.

Bioequivalence criteria:

The 90 % confidence interval of the geometric mean ratio (T/R), obtained from the ANOVA of log-transformed pharmacokinetic parameters AUC0-t and Cmax of Pomalidomide was within 80.00 % to 125.00 %.

Results

In total 40 + 2 subjects were enrolled to the Study and 40 subjects were dosed in Period 1. One participant discontinued from the Study due to adverse event in period 1. 2 subjects did not report for Period. One was not included in the Period 2 due to protocol non-compliance. Samples from 36 subjects were analysed and included in the pharmacokinetic and statistical analysis.

Table 1. Pharmacokinetic results in Study BE-2181-22

	Reference Product (R)				Test Product (T)			
Pharmacokinetic Parameter(s)	**N**	**Arithmetic mean**	**Standard deviation**	**CV (%)**	**N**	**Arithmetic mean**	**Standard deviation**	**CV (%)**
$AUC_{(0-t)}$	36	698.80	157.647	22.56	36	722.62	167.383	23.16
$AUC_{(0-inf)}$	36	713.71	163.613	22.92	36	738.50	175.226	23.73
C_{max}	36	69.00	11.931	17.29	36	74.54	13.062	17.52
*Tmax	36	2.26	0.67-4.52	-	36	2.00	0.67-4.50	-
Thalf	36	8.26	1.414	17.11	36	8.20	1.315	16.04
Kel	36	0.09	0.015	17.47	36	0.09	0.014	15.99
AUC ratio (%)	36	97.99	0.781	0.80	36	97.97	0.876	0.89
Residual Area (%)	36	2.01	0.781	38.79	36	2.03	0.876	43.13
*: Median & range reported.								

*Median (Min, Max)

Table 2. Statistical summary of the comparative bioavailability data for pomalidomide in study BE-2181-22

				90 % C.I (%)	
Pharmacokinetic Parameter(s)	**Test Geometric least square Mean**	**Reference Geometric least square Mean**	**Test/ Reference Ratio (%)**	**Lower**	**Upper**
$AUC_{(0-t)}$ (h*ng/mL)	703.28	681.61	103.18	100.14	106.31
$AUC_{(0-inf)}$ (h*ng/mL)	717.88	695.63	103.20	100.10	106.39
C_{max} (ng/mL)	73.56	68.05	108.09	104.37	111.95

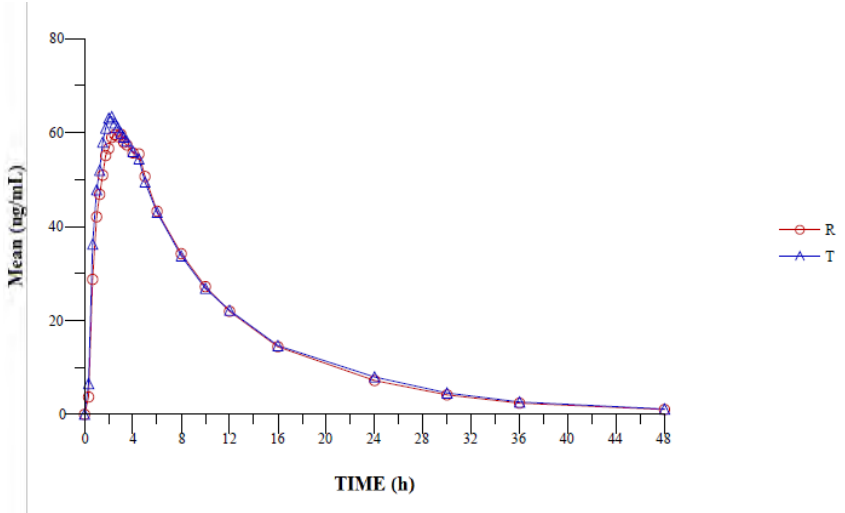
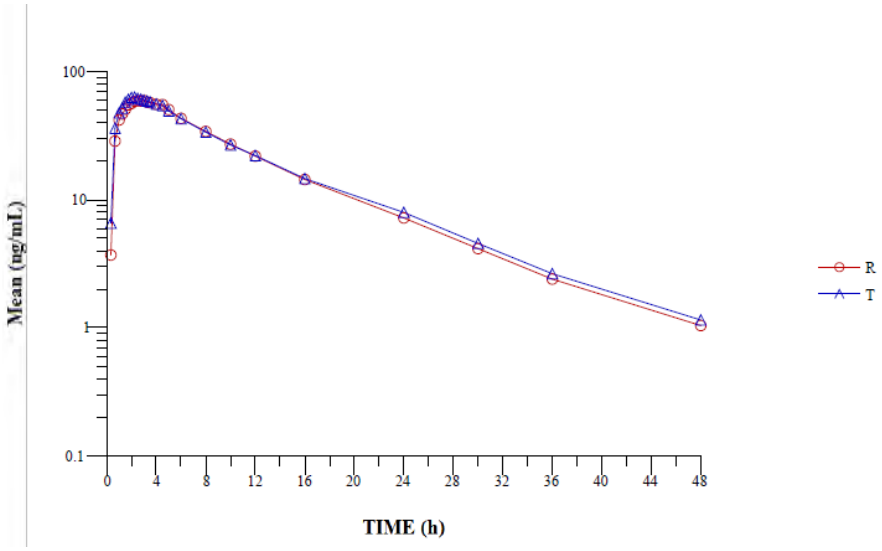


Figure 2. The linear plot of mean plasma pomalidomide concentrations vs. time in study BE-2181-22

Figure 3. The Semi-Log plot of Mean Plasma Pomalidomide Concentrations vs. Time in Study BE-2181-22



- **Safety data**

No serious adverse events or deaths were reported in the study. In total 5 adverse events were reported by 5 subjects out of 40 subjects participated throughout the study (**Table 3**).

Table 3. Reported adverse events by treatment group in Study BE-2181-22

Body System/Adverse Event*	Bioequivalence Study Study No. BE-2181-22	
	Test product (T) N (%)	Reference product (R) N (%)
Skin and subcutaneous tissue disorders		
Pruritus	-	1 (2.63%)
Musculoskeletal and connective tissue disorders		
Back pain	1 (2.63%)	1 (2.63%)
		-
General disorders and administration site conditions		
Catheter site swelling	-	1 (2.63%)
Nervous system disorders		
Headache	-	1 (2.63%)
Total (%)	**1 (2.63%)**	**4 (10.53%)**

Out of 4 AEs that occurred following administration of reference product R, 3 were considered related (possible/ probable) to the reference product and 1 was considered to not related (Unlikely) to the reference product. All AEs were mild in intensity except itching over forehead with subject no 1004 in period 1 which was moderate in intensity and were resolved without any sequelae.

Only 1 AE that occurred following administration of test product T, was considered related (possible/ probable) to the test product. AE was mild in intensity and resolved without any sequelae.

Supportive Study TVI-P8-456

A single centre, randomised, single dose, laboratory-blinded, 3-period, 3 sequence, crossover comparative bioavailability pilot study was conducted under fasting conditions on 21 healthy male subjects. The rate and extent of absorption of pomalidomide were measured and compared following a single dose (1 x 4 mg) of Test-1, Test-2 (different batches of Pomalidomide Teva 4 mg capsules) and the reference formulation (Imnovid 4 mg capsule). The drug administrations were separated by a wash-out of 7 days.

The main absorption and disposition parameters were calculated using a non-compartmental approach with a log-linear terminal phase assumption. The pharmacokinetic parameters of this trial were Cmax, Tmax, AUC0-T, AUC0-∞, AUC0-T/∞, λZ and T half. The statistical analysis was based on a parametric ANOVA model of the pharmacokinetic parameters; the two-sided 90% confidence interval of the ratio of geometric means for the Cmax, AUC0-T and AUC0-∞ was based on ln-transformed data; the Tmax was rank-transformed.

Results of this study are summarised in **Table 4** and **Table 5**.

Table 4*. Pharmacokinetic data for pomalidomide in study TVI-P8-456*

Pharmacokinetic parameter	Arithmetic Means (±CV%)		
	Test product (T1)	Test product (T2)	Reference Product (R)
AUC_{0-t}	658.109 (20.0%)	631.781 (18.0%)	628.623 (20.1%)
AUC_{0-inf}	669.195 (20.1%)	640.597 (17.9%)	637.900 (19.9%)
C_{max}	67.246 (17.1%)	66.513 (14.2%)	70.282 (18.6%)
t_{max}	2.25 (1.00 – 4.00)	2.25 (1.00 – 4.00)	2.00 (1.00 – 6.00)

Table 5. Pharmacokinetic results in study TVI-P8-456

PARAMETER	INTRA-SUBJECT C.V. (%)	GEOMETRIC LSMEANS [a]			Comparison	RATIO (%)	90% CONFIDENCE LIMITS (%)	
		TEST-1 (n=17)	TEST-2 (n=16)	REFERENCE (n=17)			LOWER	UPPER
C_{max}	8.0	66.431	66.730	69.330	Test-1 *vs* Reference	95.82	91.44	100.41
					Test-2 *vs* Reference	96.25	91.76	100.96
AUC_{0-T}	6.1	649.547	640.200	620.548	Test-1 *vs* Reference	104.67	101.02	108.46
					Test-2 *vs* Reference	103.17	99.49	106.98
$AUC_{0-\infty}$	6.1	660.369	649.515	629.926	Test-1 *vs* Reference	104.83	101.15	108.65
					Test-2 *vs* Reference	103.11	99.41	106.94

[a] units are ng/mL for C_{max} and ng·h/mL for AUC_{0-T} and $AUC_{0-\infty}$

No new concerning safety finding were reported in the study. No subject was withdrawn by the investigator for safety reasons. A total of 12 adverse events were reported by 7 (33%) of the 21 subjects who participated in this study. Of these adverse events, 7 were experienced after administration of Test-1, 4 following administration of Test-2, and 1 following administration of the Reference product.

2.4.2.2. Pharmacodynamics

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

2.4.3. Discussion on clinical aspects

This application does not contain any new data on pharmacodynamics, efficacy and safety of the active substance. However, the summary of the available data provided by the applicant is considered sufficient.

The pivotal study in support of this application is Study BE-2181-22, an open label, randomised, single dose, two-way crossover, bioequivalence study designed to evaluate the bioequivalence of pomalidomide 4mg between a test product Pomalidomide 4mg hard capsules and a reference product Imnovid 4 mg hard capsules in healthy volunteers under fasting conditions.

The overall design of the study is considered acceptable. The washout period of 7 days is appropriate. The chosen time points for blood samples collection are acceptable. The choice of the EU reference product is appropriate. The achiral analytical method was employed for this study which was validated and most of the recommended parameters met the acceptance criteria.

The primary plasma pomalidomide PK parameters were Cmax and AUC0-t, and secondary parameters were AUCinf, Tmax, Kel, and Thalf. All parameters were estimated using a non-compartmental approach.

Study subjects were administered the dose of the highest applied strength of 4 mg, which is in line with CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Pomalidomide 4 mg hard capsules met the protocol-defined criteria for bioequivalence when compared with the reference product Imnovid 4mg. 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 80.00% to 125.00%. Bioequivalence of the two formulations was demonstrated.

No serious adverse events were reported during the conduct of this study.

The applicant also submitted results from a supportive, open-label, single dose, crossover, comparative bioavailability pilot study TVI-P8-456 with Pomalidomide 4 mg capsules in healthy male volunteers in fasting state. The reference product in this study was Imnovid 4 mg capsule. The objective of this study was to estimate the intra-subject CV, each Test to Reference ratio (Test-1 *vs* Reference and Test-2 *vs* Reference). The drug administrations were separated by a wash-out of 7 days.
The overall design of the study is considered acceptable. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. Pharmacokinetic and statistical methods applied were adequate.

The results showed that the intra-subject coefficients of variation were 8.0%, 6.1% and 6.1% for Cmax, AUC0-T and AUC0-∞, respectively. For both comparisons, the Test to Reference ratio of geometric LSmeans and corresponding 90% confidence interval for the Cmax, AUC0-T and AUC0-∞ were all within the 80.00 to 125.00% range. No new concerning safety finding were reported in the study.

Based on these results, Pomalidomide Teva 4 mg capsules, hard and Reference Imnovid 4 mg hard capsules are bioequivalent after single-dose administration under fasting condition.

The requested biowaiver for the additional strengths 1mg, 2 mg and 3 mg strengths is considered acceptable.

2.4.4. Conclusions on clinical aspects

Based on the presented bioequivalence study BE-2181-22 Pomalidomide Teva 4 mg hard capsules can be considered bioequivalent with Imnovid 4mg hard capsules.

The results of study BE-2181-22 with 4mg formulation can be extrapolated to other strengths 1mg, 2mg, 3mg, according to conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1, section 4.1.6.

2.5. Risk Management Plan

2.5.1. Safety concerns

Table 6. Summary of safety concerns

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

2.5.2. Pharmacovigilance plan

Activity and status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3-Required additional pharmacovigilance activities				
Monitoring of pregnancy prevention programme (PPP) Ongoing	An annual evaluation of effectiveness of pomalidomide PPP through evaluation report done on a global level for all countries where measures are required by relevant NCA. Two categories of indicators would be considered: process indicators (distribution metrics), and outcome indicators (reporting rates and analysis of spontaneous post marketing reports of adverse drug reactions of interest).	Teratogenicity	Annual evaluation report	TBD – after agreement with respective NCA on methods and design Periodically as of launch, in accordance with PSUR schedule

2.5.3. Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
IMPORTANT IDENTIFIED RISKS		
Teratogenicity	**Routine risk minimisation measures:** SmPC sections 4.3, 4.4, 4.6, 4.8 and 5.3. PL section 2. Legal status. **Additional risk minimisation measures:** Pregnancy Prevention Programme: 1. Educational Programme consisting of:	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Expedited reporting of all pregnancies and abnormal pregnancy test results. Pregnancy specific questionnaires for collection of detailed initial and follow up information for pregnancies. Follow-up of abnormal pregnancy test results

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	a. The Educational Healthcare Professional's Kit to include educational healthcare professional brochure, educational brochures for patients, patient card, risk awareness forms, and information on where to find latest SmPC. 2. Therapy management a. Criteria for determining women of childbearing potential, contraceptive measures and pregnancy testing for women of childbearing potential. b. Advice in SmPC and educational materials. 3. System to ensure appropriate measures have been completed. a. Patient Card to document childbearing status, counselling and pregnancy testing.	Follow-up of all pregnancies until outcome is known. Follow-up of infant until one year after delivery. Root cause analysis of failed PPP as part of standard follow-up. **Additional pharmacovigilance activities:** Monitoring of pregnancy prevention programme (PPP) implementation and compliance on a country basis in agreement with the relevant NCA (i.e., monitoring of Patient Card completion).
Severe infection due to neutropenia and pancytopenia	**Routine risk minimisation measures:** SmPC section 4,2, 4.4 and 4.8. PL section 2 and 4. Legal status. **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** If there is a change in nature or frequency observed or significant clinical findings emerge, these events will be analysed in the PSURs. Event specific questionnaire for the collection of the AE and follow-up. **Additional pharmacovigilance activities:** None.
Thrombocytopenia and bleeding	**Routine risk minimisation measures:** SmPC section 4.2, 4.4 and 4.8. PL sections 2 and 4.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Legal status. **Additional risk minimisation measures:** Educational HCP brochure Educational brochure for patients	If there is a change in nature or frequency observed or significant clinical findings emerge, these events will be analysed in the PSURs. Event specific questionnaire for the collection of the AE and follow-up. **Additional pharmacovigilance activities:** None.
Cardiac failure	**Routine risk minimisation measures:** SmPC section 4.4 and 4.8. PL sections 2 and 4. Legal status. **Additional risk minimisation measures:** Educational HCP brochure	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** If there is a change in nature or frequency observed or significant clinical findings emerge, these events will be analysed in the PSURs. Event specific questionnaire for the collection of the AE and follow-up. **Additional pharmacovigilance activities:** None.
Non-melanoma skin cancer	**Routine risk minimisation measures:** SmPC section 4.4 and 4.8. PL section 2 and 4. Legal status. **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** If there is a change in nature or frequency observed or significant clinical findings emerge, these events will be analysed in the PSURs. Event specific questionnaire for the collection of the AE and follow-up. **Additional pharmacovigilance activities:** None.
IMPORTANT POTENTIAL RISKS		
Other second primary malignancies	**Routine risk minimisation measures:** SmPC section 4.4 and 5.3. PL section 2. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** If there is a change in nature or frequency observed or significant clinical findings emerge, these events will be analysed in the PSURs. Event specific questionnaire for the collection of the AE and follow-up. **Additional pharmacovigilance activities:** None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Cardiac arrhythmias	**Routine risk minimisation measures:** SmPC section 4.8. PL section 4. Legal status. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** If there is a change in nature or frequency observed or significant clinical findings emerge, these events will be analysed in the PSURs. Event specific questionnaire for the collection of the AE and follow-up. **Additional pharmacovigilance activities:** None.
MISSING INFORMATION		
None		

2.5.4. Conclusion

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

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

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, 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; 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 as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The bioequivalence study BE-2181-22 forms the pivotal basis with an open-label, single-dose, randomised, two-period, two-treatment, two-sequence, crossover design in healthy volunteers under fasting conditions to evaluate the bioequivalence between the test product Pomalidomide Teva 4mg hard capsules and the reference product Imnovid 4 mg hard capsules.
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 Teva 4mg hard capsules met the protocol-defined criteria for bioequivalence when compared with Imnovid 4mg hard capsule. The point estimates and their 90% confidence intervals for the parameters AUC0-t, AUC0-72h, 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.

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

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

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Pomalidomide Teva 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. See appendix.

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 Teva is favourable in the following indication:

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

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

Conditions or restrictions regarding supply and use

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

Other conditions and requirements of the marketing authorisation

- ***Periodic Safety Update Reports***

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

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

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

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

- **Additional risk minimisation measures**

1. The MAH shall agree the details of a controlled access programme with the National Competent Authorities and must implement such programme nationally to ensure that:
   - Prior to prescribing (where appropriate, and in agreement with the National Competent Authority, dispensing) all healthcare professionals who intend to prescribe (and dispense) pomalidomide are provided with an Educational Healthcare Professional's Kit containing the following:
     - Educational Healthcare Professional brochure
     - Educational brochures for patients
     - Patient card
     - Risk awareness forms
     - Information on where to find latest Summary of Product Characteristics (SmPC).
2. The MAH shall implement a pregnancy prevention programme (PPP) in each Member State. Details of the PPP should be agreed with the National Competent Authorities in each Member State and put in place prior to the launch of the medicinal product.
3. The MAH should agree the contents of the Educational Healthcare Professional's Kit with the National Competent Authority in each Member State prior to launch of the medicinal product and ensure that the materials contain the key elements as described below.
4. The MAH should agree on the implementation of the controlled access programme in each Member State.

Key elements to be included

The Educational Healthcare Professional's Kit

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

Educational Healthcare Professional brochure

- Brief background on pomalidomide
- Maximum duration of treatment prescribed
  - 4 weeks for women with childbearing potential
  - 12 weeks for men and women without childbearing potential
- The need to avoid foetal exposure due to teratogenicity of pomalidomide in animals and the expected teratogenic effect of pomalidomide in humans
- Guidance on handling the blister or capsule of Pomalidomide Teva for healthcare professionals and caregivers
- Obligations of the healthcare professionals 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

- Description of the PPP and categorisation of patients based on sex and childbearing potential
  - Algorithm for implementation of PPP
  - Definition of women of childbearing potential (WCBP) and actions the prescriber should take if unsure
- Safety advice for women of childbearing potential
  - The need to avoid foetal exposure
  - Description of the PPP
  - Need for effective contraception (even if the woman has amenorrhoea) and definition of effective contraception
  - That if she needs to change or stop using her method of contraception she should inform:
    - The physician prescribing her contraception that she is on pomalidomide
    - The physician prescribing pomalidomide that she has stopped or changed her method of contraception
  - Pregnancy test regime
    - Advice on suitable tests
    - Before commencing treatment
    - During treatment based on method of contraception
    - After finishing treatment
  - Need to stop pomalidomide immediately upon suspicion of pregnancy
  - Need to tell treating doctor immediately upon suspicion of pregnancy

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

        - For at least 7 days following final dose
    - That he should not donate semen or sperm during treatment (including during dose interruptions) and for at least 7 days following discontinuation of pomalidomide 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 patient
    - Need to refer patient to physician specialised or experienced in dealing with teratology and its diagnosis for evaluation and advice
    - Local contact details for reporting of any suspected pregnancy immediately
    - Pregnancy reporting form

- Local contact details for reporting adverse reactions

Educational Brochures for patients

The Educational brochures for patients should be of 3 types:

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

All educational brochures for patients should contain the following elements:

- That pomalidomide is teratogenic in animals and is expected to be teratogenic in humans
- That pomalidomide may cause thrombocytopenia and the need for regular blood tests
- Description of the patient card and its necessity
- Guidance on handling pomalidomide 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 treatment (including during dose interruptions) and for at least 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
- The need for effective contraception and definition of effective contraception
- That if she needs to change or stop using her method of contraception she should inform:
    - The physician prescribing her contraception that she is on pomalidomide
    - The physician prescribing pomalidomide that she has stopped or changed her method of contraception
- Pregnancy test regime
    - Before commencing treatment
    - During treatment (including dose interruptions), at least every 4 weeks except in case of confirmed tubal sterilisation
    - After finishing treatment

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

Brochure for male patients

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

        - the physician prescribing pomalidomide 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 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
    - 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
    - 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
    - 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 card
     - Risk awareness forms
     - Information on where to find latest Summary of Product Characteristics (SmPC).
2. The MAH shall implement a pregnancy prevention programme (PPP) in each Member State. Details of the PPP should be agreed with the National Competent Authorities in each Member State and put in place prior to the launch of the medicinal product.
3. The MAH should agree the contents of the Educational Healthcare Professional's Kit with the National Competent Authority in each Member State prior to launch of the medicinal product and ensure that the materials contain the key elements as described below.
4. The MAH should agree on the implementation of the controlled access programme in each Member State.

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- 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 Teva for healthcare professionals and caregivers
- Obligations of the healthcare professionals 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

- Description of the PPP and categorisation of patients based on sex and childbearing potential
  - Algorithm for implementation of PPP
  - Definition of women of childbearing potential (WCBP) and actions the prescriber should take if unsure
- Safety advice for women of childbearing potential
  - The need to avoid foetal exposure
  - Description of the PPP
  - Need for effective contraception (even if the woman has amenorrhoea) and definition of effective contraception
  - That if she needs to change or stop using her method of contraception she should inform:
    - The physician prescribing her contraception that she is on pomalidomide
    - The physician prescribing pomalidomide that she has stopped or changed her method of contraception
  - Pregnancy test regime
    - Advice on suitable tests
    - Before commencing treatment
    - During treatment based on method of contraception
    - After finishing treatment
  - Need to stop pomalidomide immediately upon suspicion of pregnancy
  - Need to tell treating doctor immediately upon suspicion of pregnancy

- Safety advice for men
  - The need to avoid foetal exposure
  - The need to use condoms if sexual partner is pregnant or a WCBP not using effective contraception (even if the man has had a vasectomy)
    - During pomalidomide treatment
    - For at least 7 days following final dose
  - That he should not donate semen or sperm during treatment (including during dose interruptions) and for at least 7 days following discontinuation of pomalidomide 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 patient
  - Need to refer patient to physician specialised or experienced in dealing with teratology and its diagnosis for evaluation and advice
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- 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 treatment (including during dose interruptions) and for at least 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
- The need for effective contraception and definition of effective contraception
- That if she needs to change or stop using her method of contraception she should inform:
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    - 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 not using effective contraception (even if the man has had vasectomy)
    - During pomalidomide treatment (including dose interruptions)
    - For at least 7 days following final dose
- That if his partner becomes pregnant he should inform his treating doctor immediately
- That he should not donate semen or sperm during treatment (including during dose interruptions) and for at least 7 days 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
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- 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
        - the physician prescribing pomalidomide 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 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
    - 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
    - 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
- 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.