COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Pomalidomide Synthon 1 mg, 2 mg, 3 mg and 4 mg, hard capsules (pomalidomide)

NL/H/5832/001-004/DC

Date: 30 December 2025

This module reflects the scientific discussion for the approval of Pomalidomide Synthon 1 mg, 2 mg, 3 mg and 4 mg, hard capsules. The procedure was finalised on 31 May 2024. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Pomalidomide Synthon 1 mg, 2 mg, 3 mg and 4 mg, hard capsules, from Synthon B.V.

The product is indicated for:

The product 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.

The product 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.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this decentralised procedure, essential similarity is proven between the new product and the innovator product Imnovid 1 mg, 2 mg, 3 mg and 4 mg, hard capsules, which have been registered in the EEA by Bristol-Myers Squibb Pharma EEIG via a centralised procedure (EU/1/13/850) since 5 August 2013.

The concerned member states (CMS) involved in this procedure for the 1 mg, 2 mg and 3 mg strengths were Austria, Finland, Greece, Iceland, Poland, Romania and Sweden.
The concerned member states (CMS) involved in this procedure for the 4 mg strength were Austria, Finland, Greece, Hungary, Iceland, Poland, Romania and Sweden.

Similarity assessment
According to Article 8(1) of Regulation (EC) No 141/2000, no marketing authorisation can be granted for a product similar to an orphan medicinal product for a period of ten years, when this concerns a similar medicinal product with the same therapeutic indication. A similarity assessment has been performed between Pomalidomide Synthon and the current orphan products authorised in the EU. These orphan products are:

Indicated for the treatment of multiple myeloma:

- Abecma (idecabtagene vicleucel), Bristol-Myers Squibb Pharma EEIG, EU/1/21/1539 orphan designation number EU/3/17/1863
- Blenrep (belantamab mafodotin), GlaxoSmithKline (Ireland) Limited, EU/1/20/1474 orphan designation number EU/3/17/1925
- Carvykti (ciltacabtagene autoleucel), Janssen-Cilag International NV, EU/1/22/1648 orphan designation number EU/3/20/2252

- Darzalex (daratumumab), Janssen-Cilag International NV, EU/1/16/1101
  orphan designation number EU/3/13/1153
- Farydak (panobinostat), zr pharma& GmbH, EU/1/15/1023
  orphan designation number EU/3/12/1063
- Kyprolis (carfilzomib), Amgen Europe B.V., EU/1/15/1060
  orphan designation number EU/3/08/548
- Ninlaro (ixazomib), Takeda Pharma A/S, EU/1/16/1094
  orphan designation number EU/3/11/899
- Talvey (talquetamab), Janssen-Cilag International NV, EU/1/23/1748
  orphan designation number EU/3/21/2486

The assessment included the comparison of the therapeutic indication, mechanism of action and principal (molecular) structure. The (updated) similarity assessment report was completed in March 2024. After consideration of the MAH arguments, Pomalidomide Synthon is not considered similar to the orphan products with regard to the mechanism of action and principal molecular structure.
Therefore, with reference to Article 8 of Regulation (EC) No. 141/2000, the existence of any market exclusivity for Abecma, Blenrep, Carvykti, Darzalex, Farydak, Kyprolis, Ninlaro and Talvey does not prevent the granting of the marketing authorisation of Pomalidomide Synthon.

II. QUALITY ASPECTS

II.1 Introduction

Pomalidomide Synthon is a hard capsule. Each capsule contains as active substance 1 mg, 2 mg, 3 mg or 4 mg pomalidomide.

The four different capsule strengths can be distinguished from each other by colour, print and length:
The 1 mg hard capsule has a yellow body and red cap, with “PLM 1” printed axial rectified in white in the body. The capsule has a length of approximately 14.3 mm.
The 2 mg hard capsule has an orange body and red cap, with “PLM 2” printed axial rectified in white in the body. The capsule has a length of approximately 18 mm.
The 3 mg hard capsule has a turquoise body and red cap, with “PLM 3” printed axial rectified in white in the body. The capsule has a length of approximately 18 mm.
The 4 mg hard capsule has a dark blue body and red cap, with “PLM 4” printed axial rectified in white in the body. The capsule has a length of approximately 18 mm.

The excipients are:
Capsule contents (for all four strengths) - cellulose, microcrystalline (E460), maltodextrin and sodium stearyl fumarate
Capsule cap (for all four strengths) - gelatine, titanium dioxide (E171). iron oxide yellow (E172) and iron oxide red (E172)

Printing ink (for all four strengths) - *s*hellac glaze ~45% (20% esterified), titanium dioxide (E171) and propylene glycol
Capsule body
1 mg hard capsule - gelatine, titanium dioxide (E171) and iron oxide yellow (E172)
2 mg hard capsule - gelatine, titanium dioxide (E171), iron oxide yellow (E172) and iron oxide red (E172)
3 mg hard capsule - gelatine, titanium dioxide (E171) and indigo carmine aluminium lake (E132)
4 mg hard capsule - gelatine, titanium dioxide (E171), iron oxide yellow (E172), indigo carmine aluminium lake (E132) and erythrosine (E127)

The capsule fill is dose proportional.

The capsules are packed in oriented polyamide (oPA)/Aluminium/ polyvinyl chloride (PVC)/Aluminium blisters.

II.2 Drug Substance

The active substance is pomalidomide, an established active substance not described in the European, US or British Pharmacopoeia. Pomalidomide is a yellow powder. Pomalidomide is slightly soluble in acetone, acetonitrile, methylene chloride, methyl ethyl ketone, and tetrahydrofuran. It is very slightly soluble in ethanol, ethyl acetate, methanol, 2-propanol, and toluene and practically insoluble in water. The active substance is chiral and is marketed as a racemic mixture. Pomalidomide shows no polymorphism.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The manufacturing process comprises two linear chemical stages with two chemical transformations. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised and the manufacturing process is described in sufficient detail.

Quality control of drug substance
The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for three commercial scale batches.

Stability of drug substance
Based on the data in the ASMF, a retest period could be granted of 60 months when stored under the stated conditions.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified, and their functions explained. The excipients are mixed and filled in capsule shells.
The development studies support that micronised drug substance should be used.
The final formulation was used in the bioequivalence (BE) study. To support the results obtained in the BE-study, the MAH has performed comparative dissolution studies in three different pH media (0.1 N HCL, pH 4.5 and pH 6.8). Comparative dissolution studies are also presented to support the biowaiver of strength. See section IV.
Overall, the pharmaceutical development of the product has been adequately performed.

Manufacturing process
Due to the low amount of active substance per capsule, the finished product is considered a specialised pharmaceutical dose form, which therefore renders the manufacturing process non-standard. The manufacturing process consists of the following steps: initial blend, final blend, lubricated blend, encapsulation, and packaging. The same blend is used for all four strengths. The manufacturing process has been validated according to relevant European/ICH guidelines.
Process validation data on the product have been presented for three full scale batches per strength in accordance with the relevant European guidelines.

Control of excipients
The excipients comply with Ph. Eur. requirements. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, water content, dissolution, uniformity of dosage units, identity, assay, impurities, and microbiological contamination. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from the proposed production site have been provided on three batches per strength, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for three batches per strength stored at 25°C/ 60% RH (36 months) and 40°C/75% RH (6 months) in accordance with applicable European guidelines. No changes were observed at long term or accelerated conditions when

packed in commercial packaging. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. On basis of the data submitted, a shelf life was granted of 36 months. No specific storage conditions needed to be included in the SmPC or on the label.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM for gelatine have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Pomalidomide Synthon has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Pomalidomide Synthon is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Imnovid which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was 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. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Pomalidomide is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The member states agreed that no further clinical studies are required, besides one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Pomalidomide Synthon 4 mg, hard capsules (Synthon B.V., the Netherlands) was compared with the pharmacokinetic profile of the reference product Imnovid 4 mg, hard capsules (Bristol-Myers Squibb Pharma EEIG, Ireland).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution study results and composition. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

Biowaiver

The following general requirements were met for the waiver for additional strength, according to the EMA Bioequivalence guideline:

a. All strengths are manufactured by the same process
b. The qualitative composition of the different strengths is the same
c. The composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths

The dissolution was investigated according to the EMA Bioequivalence guideline. The f_2 similarity factor values were calculated for the 1 mg, 2 mg and 3 mg strengths, each of them compared to the 4 mg strength at three pH values (pH 1.2, pH 4.5 and pH 6.8). Not all values were within criteria (>50%). An f_2 value between 50 and 100% suggests that the dissolution profiles of the two compared dissolution profiles are similar. The similarity calculations supported similarity of the dissolution profiles for all strength, and the biowaiver of strength was accepted.

Bioequivalence study

Design

A single-dose, open label, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 38 healthy male subjects, aged 20-59 years. Each subject received a single dose (4 mg) of one of the two pomalidomide formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least ten hours. There were two dosing periods, separated by a washout period of seven days.

Blood samples were collected pre-dose and at 0.33, 0.66, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 24, 36 and 48 hours after administration of the products.

The design of the study is acceptable.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
38 Subjects were enrolled in the study. One subject was withdrawn due to personal reasons. In total 37 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of pomalidomide, 4 mg under fasted conditions.

Treatment N=37	**AUC_{0-t}** (ng.h/mL)	**$AUC_{0-\infty}$** (ng.h/mL)	**C_{max}** (ng/mL)	**t_{max}** (h)
Test	506.2 ± 153.0	517.3 ± 155.6	53.4 ± 11.0	3.00 (1.50 - 6.00)
Reference	508.8 ± 161.2	523.5 ± 160.0	59.4 ± 12.5	2.00 (0.67 - 5.50)
***Ratio (90% CI)**	1.00 (0.97 - 1.03)	--	0.90 (0.86 - 0.94)	

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to t = 48 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Conclusion on bioequivalence study:
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Pomalidomide Synthon 4 mg is considered bioequivalent with Imnovid 4 mg.

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

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Pomalidomide Synthon. At the time of approval, the most recent version of the RMP was version 3.0 with date of sign-off 26 March 2024.

Table 2. Summary table of safety concerns as approved in RMP

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

The routine pharmacovigilance and risk minimisation measures, the safety information and the product information are aligned to the reference medicinal product Imnovid and are acceptable.

At the time of approval of this product, it was considered that a pregnancy prevention programme (PPP) should be implemented and monitored as additional pharmacovigilance activity to investigate risks of teratogenicity, in line with the reference product.

Besides routine risk minimisation measures, the MAH provided additional risk minimisation measures (aRMM) for all the safety concerns as mentioned in Table 2, in a controlled access program. The aRMM consist of HCP Educational Materials and Patient Educational Materials. The educational Healthcare Professional's Kit must contain the following key elements:

- Educational Healthcare Professional brochure
- Educational brochures for patients
- Patient card
- Risk awareness forms
- Information where to find the latest Summary of Product Characteristics (SmPC)

Overall, the safety specification, additional pharmacovigilance activities and additional risk minimisation measures are considered to be in line with the RMP of the reference product Imnovid (version 17.0) and are acceptable.

The MAH shall implement and monitor a pregnancy preventing 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. Safety updates will be submitted with future PSURs (as required per EURD list).

The MAH shall agree the final text of 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 all key elements.
The MAH shall agree on the details and the implementation of the controlled access programme in each member state prior to launch of the medicinal product.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Imnovid. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference for the content and safety issues to Imnovid 1 mg, 2 mg, 3 mg and 4 mg hard capsules (EU/1/13/850). The PL of Pomalidomide Synthon covers all four strengths, as the key safety information is identical for all four strengths. This is in accordance with the PL of the reference product. For the layout, house style and formulation, reference is made to the full user testing report by the MAH of the PL of Clozapine 12.5 mg orodispersable tablets.
The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Pomalidomide Synthon 1 mg, 2 mg, 3 mg and 4 mg, hard capsules have a proven chemical-pharmaceutical quality and are a generic forms of Imnovid 1 mg, 2 mg, 3 mg and 4 mg, hard capsules. Imnovid is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Pomalidomide Synthon with

the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 31 May 2024.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
-	-	-	-	-	-