21 July 2022
EMA/773068/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Thalidomide Lipomed

International non-proprietary name: thalidomide

Procedure No. EMEA/H/C/005715/0000

Note

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

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List of abbreviations

AS: Active Substance

ASMF: Active Substance Master File

ATC Anatomical therapeutic chemical classification system

BCS Biopharmaceutics classification system

BE Bioequivalence

BSE Bovine spongiform encephalopathy

CFU Colony-forming unit

CoA Certificate of analysis

CQAs Critical quality attributes

EU European Union

FP Finished product

GC Gas chromatography

GMP Good Manufacturing Practice

HPLC High Performance Liquid Chromatography

ICH International Conference on Harmonisation

ICP AES Inductively coupled plasma atomic emission spectroscopy

IPC In-process controls

IR Infra-Red Spectroscopy

QbD Quality by design

QTPP Quality target product profile

MAH Marketing Authorisation Holder

MO major objection

MS Mass Spectrometry

NLT Not Less Than

NMR Nuclear Magnetic Resonance

NMT Not More Than

OOS Out of specification

Ph.Eur. European Pharmacopoeia

PVC Polyvinylchloride

RH Relative humidity

RPM Rotation per minute

SmPC Summary of Product Characteristics

TSE: Transmissible spongiform encephalopathy

USP United States Pharmacopoiea

UV Ultraviolet Spectroscopy

XRD X-ray diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Lipomed GmbH submitted on 1 April 2021 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Thalidomide Lipomed, 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 July 2020.

The application concerns a hybrid medicinal product as defined in Article 10(3) 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:

Thalidomide Lipomed in combination with melphalan and prednisone is indicated as first line treatment of patients with untreated multiple myeloma, aged ≥ 65 years or ineligible for high dose chemotherapy.

Thalidomide Lipomed is prescribed and dispensed in accordance with the Thalidomide Lipomed Pregnancy Prevention Programme (see section 4.4 of the SmPC).

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 10(3) of Directive 2001/83/EC

The application submitted is composed of administrative information, complete quality data and at least a bioequivalence study with the reference medicinal product Thalidomide BMS instead of non-clinical and clinical data 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: Thalidomide Celgene 50 mg capsule, hard (currently Thalidomide BMS)
- Marketing authorisation holder: Celgene Europe B.V. (currently Bristol-Myers Squibb)
- Date of authorisation: 16-04-2008
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/08/443/001

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

- Product name, strength, pharmaceutical form: Thalidomide Celgene 50 mg capsule, hard (currently Thalidomide BMS)
- Marketing authorisation holder: Celgene Europe B.V. (currently Bristol-Myers Squibb)
- Date of authorisation: 16-04-2008
- Marketing authorisation granted by:

  - Union
- Marketing authorisation number: EU/1/08/443/001

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: Thalidomide Celgene 50 mg capsule, hard (currently Thalidomide BMS)
- Marketing authorisation holder: Celgene Europe B.V. (currently Bristol-Myers Squibb)
- Date of authorisation: 16-04-2008
- Marketing authorisation granted by:

  - Union
- Marketing authorisation number: EU/1/08/443/001
- Bioavailability study number(s): 2020-002445-42

1.3. Information on Paediatric requirements

Not applicable.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

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

1.5. Scientific advice

The applicant received the following Scientific Advice on the development relevant for the approved indication from the CHMP:

Date	**Reference**	**SAWP co-ordinators**
30/04/2020	EMEA/H/C/005715/0000	Adriana Andric, Flora Musuamba Tshinanu and Brigitte Schwarzer-Daum

The Scientific Advice pertained to the following quality and clinical aspects:

- the *in vitro* dissolution testing;
- the adequacy of a three-way, three-sequence crossover bioavailability study design to compare Myrin 50 mg, Thalidomide Celgene 50 mg and Myrin 100 mg and demonstrate the bioequivalence of the generic medicinal product Myrin 50 mg and the dose proportionality of the 'hybrid' medicinal product Myrin 100 mg;
- the choice of the primary and secondary objectives for the 'hybrid' medicinal product Myrin 100 mg coated tablets in the planned bioavailability study, as well as the statistical assumptions for the sample size estimation and the proposed washout period;
- the use of an achiral bioanalytical method;
- draft proposal of similarity assessment report for Module 1.7.1.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Simona Badoi Co-Rapporteur: Hrefna Gudmundsdottir

The application was received by the EMA on	1 April 2021
The procedure started on	20 May 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	9 August 2021
The CHMP Co-Rapporteur's critique Assessment Report was circulated to all CHMP and PRAC members on	23 August 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	23 August 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	16 September 2021
The applicant submitted the responses to the CHMP consolidated List of Questions on	4 March 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	26 April 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	5 May 2022
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	19 May 2022
The applicant submitted the responses to the CHMP List of Outstanding Issues on	20 June 2022

The CHMP Rapporteurs 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	6 July 2022
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 Thalidomide Lipomed on	21 July 2022
The CHMP adopted a report on similarity of Thalidomide Lipomed with Kyprolis (carfilzomib), Imnovid (pomalidomide), Ninlaro (ixazomib), Farydak (panobinostat), Darzalex (daratumumab), Blenrep (belantamab mafodotin), Abecma (idecabtagene vicleucel), Carvykti (ciltacabtagene autoleucel)	21 July 2022

2. Scientific discussion

2.1. Introduction

This application for marketing authorisation concerns a 'hybrid' application, change in strength, to a centrally authorised medicinal product according to Art. 10(3) of Directive 2001/83/EC as amended, supported by published data and a bioequivalence study. The application refers to the reference product, Thalidomide Celgene 50 mg, capsule, hard, from Celgene Europe B.V. Netherlands (currently known as Thalidomide BMS, from Bristol-Myers Squibb). The eligibility of Thalidomide Lipomed was confirmed in July 2020.

The community marketing authorisation of the reference has been granted on 16 April 2008 under number EU/1/08/443/001.

The applicant has developed Thalidomide Lipomed 100 mg coated tablet as hybrid to the reference medicinal product, Thalidomide Celgene 50 mg capsule. The difference from the reference product consists of the change in the strength.

The indications, posology and pharmacology as presented in the proposed SmPC are in line with the originator product's SmPC.

Therapeutic indication

Thalidomide Lipomed in combination with melphalan and prednisone is indicated as first line treatment of patients with untreated multiple myeloma, aged ≥ 65 years or ineligible for high dose chemotherapy.

Thalidomide Lipomed is prescribed and dispensed in accordance with the Thalidomide Lipomed Pregnancy Prevention Programme (see section 4.4 of the SmPC).

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as coated tablets containing 100 mg of thalidomide as active substance.

Other ingredients are:

- in tablet core: lactose monohydrate, copovidone (E 1208), talc (E 553b), magnesium stearate (E 470b), microcrystalline cellulose [E 460(i)],

- in coating layer: heavy kaolin (E 559), sucrose, acacia (E 414), calcium carbonate (E 170), talc (E 553b), titanium dioxide (E 171).

The product is available in PVC-Al 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 thalidomide is 2-(2,6-dioxopiperidin-3-yl)-2,3-dihydro-1H-isoindole-1,3-dione, corresponding to the molecular formula $C_{13}H_{10}N_2O_4$. It has a relative molecular mass of 258.23 g/mol and the structure shown in Figure 1.

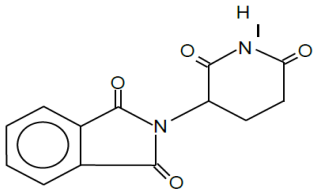

Figure 1: Active substance structure

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

Thalidomide is white to almost white non-hygroscopic, crystalline powder. It is practically insoluble in water, ethanol, methanol and chloroform.

Thalidomide has one chiral centre, derived from glutamic acid. However, this stereogenic centre has exacerbated lability and is easily epimerized in the reaction conditions used. This lability is related to the presence of the carbonyl and imide groups at the stereogenic centre position α. Therefore, it can exist as two enantiomers: R and S. The specific optical rotation specification proposed is consistent with the preparation of a racemic product.

Thalidomide exists in two crystal forms: α and β as shown by x-rays analysis.

2.2.2.1. Manufacture, characterisation and process controls

The active substance (AS) is produced by chemical synthesis. The manufacturing process consists of two steps (the reaction step and the purification step) with one isolated intermediate. The typical thalidomide batch size has been stated. Following a Major Objection (MO) raised by the CHMP, the selection of the starting materials has been justified according to the guidelines and information has been provided confirming they are sufficiently controlled.

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

Thalidomide is crystallised as ß polymorph form; A test for the identification of the polymorphic form has been included in the AS specification.

Critical process parameters are clearly identified and adequate justified by the ASMF holder. Appropriate in-process controls were presented. Information about re-processing is provided.
Specifications for all other materials used in the manufacturing process have been provided, together with description of the analytical methods and certificates of analysis.

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 including genotoxic impurities were well discussed with regards to their origin and characterised.

During the procedure an MO was raised by the CHMP requesting a complete synthetic scheme including also the purification step as per the Guideline on the chemistry of active substances EMA/454576/2016) and demonstration that impurities from starting materials and other raw materials are not carried over into the final AS. The applicant provided the updated synthetic scheme and discussed the potential impurities from the starting materials as requested. It was concluded that the impurities from starting materials that might potentially be carried over into the final active substance are sufficiently addressed by the existing control strategy and that no further controls are necessary. It has been demonstrated that the impurities are adequately controlled during manufacturing of the active substance. The MO was thus resolved.

The manufacturing process of thalidomide was validated on three commercial batches.

The AS is packaged in a container closure system for which a brief description and specifications were provided. Certificates of analysis for the packaging materials have been presented. The materials comply with the relevant European requirements.

2.2.2.2. Specification

The active substance specification applied by the finished product manufacturer includes appropriate tests and limits for appearance (visual), identity (IR, UV), colour of test solution (Ph. Eur.), loss on drying (Ph. Eur.), optical rotation (Ph. Eur.), impurities (HPLC), assay (HPLC), particle size distribution (laser diffraction, Ph. Eur.) and microbiological quality (Ph. Eur.).

Test parameters and acceptance criteria are in accordance with the ICH Q6A guideline and in line with general pharmaceutical practice and experience. Impurities limits are in-line with the ICH Q3A and limits for residual solvents were established on the basis of actual data and comply with ICH Q3C requirements. Assay limits derive from the current USP monograph for thalidomide; there is no Ph. Eur. Monograph. Inorganic (elemental) impurities are controlled by the AS manufacturer.

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

Batch analytical data are provided by the manufacturer of active substance for three commercial scale batches and relevant CoAs have been presented. The batches showed compliance with the proposed specification.

2.2.2.3. Stability

Stability data on three commercial scale batches of the active substance stored in the intended commercial packaging for up to 36 months under long term conditions (25°C / 60% RH), intermediate storage condition (30°C, 65% RH) and for 6 months under accelerated conditions (40°C, 75% RH) according to the ICH guidelines were provided by the finished product manufacturer.

Samples were tested for appearance, colour of test solution, loss on drying, impurities, assay, particle size distribution and microbiological quality. Results obtained under all storage conditions met the specification at all timepoints; no trends were observed.

Additional stability data on another nine full scale thalidomide batches stored in the intended commercial packaging for up to 36 months under long term conditions (25°C / 60% RH) and for 6 months under accelerated conditions (40°C / 75% RH) according to the ICH guidelines were also provided by the AS manufacturer in the provided ASMF.

Samples were tested for the following parameters: description, color, identification, loss on drying, optical rotation, impurities, assay, microbiological tests according to the ASMF holder specifications. Results complied with the specifications.

Three active substance batches were submitted to photostability studies as per ICH guideline. From the results obtained, it is concluded that thalidomide is not photosensitive, since no significant change was observed before and after exposure to light.

Forced degradation studies have been performed under stress conditions of heat (80°C) , heat and acidic treatment, heat and alkaline treatment, UV radiation, heat and oxidation treatment, heat in water as part of the validation of the impurities testing method, to demonstrate that the method is stability indicating. Varying degree of degradation was observed ranging from no degradation under heat at 80°C, to almost complete degradation under heat and alkaline treatment.

Based on the overall presented stability results, the proposed retest period of 36 months without 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 (FP) is immediate release coated tablets containing 100 mg of thalidomide intended for oral use. The finished product is presented as white, round, domed sugar-coated tablets with diameter approx. 10.2 mm and thickness approx. 5.5 mm.

The finished product has been developed as a hybrid of the reference medicinal product Thalidomide Celgene 50 mg capsules, hard. The application was submitted in accordance with Art. 10(3) hybrid application (change in strength –quantitative change to the active substance). Consequently, the objective was to prepare coated tablets essentially similar to the reference medicinal product.

The active substance, thalidomide, is known, but is not described in the Ph. Eur. It is a stable compound and no special precaution had to be implemented during the development of the FP manufacturing process. However it is practically insoluble in water, and therefore development was focused on aspects like dissolution of the AS from the tablets and the bioequivalence vs the reference product, particle size and polymorphism. It has been shown that the AS crystalline form α does not change significantly during storage of the active substance.

The FP consists of a tablet core and sugar-coating. The core composition is a classical mix of standard excipients chosen to guarantee an immediate and complete release of the active substance. The excipients show no compatibility issues with the AS as attested by the long-term stability studies. Based on the distribution and the absorption from the digestive tract determined by the chemical properties of the AS itself, no development of the core composition were presented. The pharmaceutical form of coated tablets with sugar coating was chosen so that skin contact with the AS and the risks associated with the highly teratogenic AS are reduced.

The formulation was based on the manufacturer experience who developed the product since 2001. The documentation has since been updated in order to demonstrate compliance to the current requirements of EU legislation.

Since the coated tablets were found to be in conformity with the set specifications and showed a reproducible dissolution profile that fulfils the requirements for immediate release tablets, no further formulation development has been performed. Critical quality attributes (CQAs) of the active substance and excipients properties impacted by changes on formulation or manufacturing process and risk assessment in formulation and process variables were not discussed, but were justified based on historical development since 2001 and this was accepted.

A discussion about the qualitative formulation vis-a-vis the reference product, and justification of the pharmaceutical form of the test versus the reference medicinal product was presented. The composition of the FP was presented properly including components, its functions and references to standards. Considering also that the FP is a simple immediate release formulation, with common excipients used in many similar pharmaceutical products the level of information regarding the pharmaceutical development is considered sufficient.

All excipients used in the FP are well known, widely used as pharmaceutical excipients and comply with relevant pharmacopoeial monographs. There is no novel constituent used in the formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The main steps of the manufacturing process were summarised. The manufacturing process development identified any critical process parameters that should be monitored or controlled to ensure that the product is of the desired quality. Satisfactory information regarding the optimisation of the process parameters were presented. Regarding the coating step, information on development of this step, characteristics of the solutions used for coating and their physical characteristics was provided.

A summary of formulations used in clinical safety and efficacy and in any relevant bioavailability or bioequivalence studies was also provided. There are no differences in the manufacturing processes of the commercial product and clinical trial materials.

The development of the dissolution method was based on the physico-chemical characteristics of the active substance and the intended dose range of the formulation. Following a MO raised during the procedure about the development of the dissolution method and the associated specification limit, the applicant further justified the choice of the proposed method by providing additional information and literature references. As part of the response same MO the initially proposed dissolution specification limit was tightened in line with the *"Reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action"* (EMA/CHMP/CVMP/QWP/336031/2017). The revised dissolution acceptance criterion is acceptable. The provided information was satisfactory and the MO was resolved.

The discriminatory power of the proposed QC dissolution method was sufficiently by varying physical characteristics of AS and composition of tablets.

The applicant submitted a relative bioavailability study (refer to clinical section of the report) in order to demonstrate bioequivalence between the test and reference product. Some comparative dissolution results had been presented initially. However the CHMP requested in a MO the results of the comparative *in vitro* dissolution testing of the batches used in the bioequivalence study at three different buffers over the complete physiological pH range (pH 1.2, 4.5 and 6.8) without surfactant in line with the relevant guideline and the recommendation given during the received CHMP scientific advice. In their response the applicant provided the requested data. The dissolution profiles were found non similar but the differences were explained as per the bioequivalence guideline.

In addition the comparative *in vitro* dissolution testing of one Thalidomide Lipomed 100 mg coated tablet against two reference product 50 mg hard capsules showed no similarity in tested pH media based on $f2$ values. Considering the high relative standard deviation(RSD) values the $f2$ statistical method is not suitable and the confidence intervals for $f2$ calculation based on 90% confidence interval with the Bootstrap method would have been recommended. However, the issue was not further pursued because as per the bioequivalence guideline the *in vivo* results prevail and *in vitro* similarity studies are only complementary to the bioavailability study. Thus the MO was considered resolved.

The finished product is packed into blister strips consisting of PVC foil and aluminium foil with heat-sealing lacquer. This container closure system is considered to be suitable for storage, since it guarantees adequate tightness and since no incompatibility between the container closure system and the coated tablets are registered. Specifications, analytical methods, certificates of analysis, IR spectra were provided for all components of the primary packaging and bulk packaging have been provided. The primary packaging PVC – aluminium blister complies with Commission Regulation (EU) No 10/2011.

For the bulk package flat bags made of high-density polyethylene specification and certificate of analysis were also provided and a declaration of compliance with the Commission Regulation (EU) No 10/2011.

2.2.3.2. Manufacture of the product and process controls

The manufacturing process of Thalidomide Lipomed 100mg coated tablets takes place in two clearly stated manufacturing sites.

The manufacturing process for the coated tablets consists of the following main steps: weighing of raw materials, granulation, drying of the granulate, sieving of the dry granulate, addition and mixing of talc, magnesium stearate and microcrystalline cellulose, compression of the tablet cores and sugar coating of the tablet cores. This is a standard manufacturing process.

Narrative description for each step was presented and batch size were stated. Process parameters were included in the description of the manufacturing process. The parameters of the critical steps of the manufacturing process are monitored during standard production. The proposed in-process controls and the tests at the time of batch release guarantee that the product is in compliance with its specifications.

An ambiguity in the original documentation led the CHMP to raise a MO requesting the applicant to clarify the product manufacturing flow between the two sites and clarify whether the presented process validation data covers both sites. The applicant in their response provided additional information and clarifications. Regarding process validation, data on a minimum of 3 consecutive batches was provided according to Annex 1 on the Guideline on process validation for finished products (EMA/CHMP/QWP/749073/2016. Moreover it was confirmed that process validation studies cover all manufacturing steps used for the production of the marketed product in both manufacturing sites. Major steps of the manufacturing process have been validated by a number of studies. Based on the response the manufacturing process (standard process) was considered sufficiently validated and the MO was resolved.

Overall, it has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

2.2.3.3. Product specification

The finished product release and shelf-life specifications include appropriate tests and limits for appearance (visual), shape (visual), diameter and thickness (calliper rule), average mass (gravimetry), dissolution (Ph. Eur. - HPLC), identity of AS (HPLC, UV), identity of colouring agent TiO_2 (ICP-AES), assay (HPLC), ethanol (GC), resistance to crushing (Ph. Eur.), content uniformity (Ph. Eur.), impurities (HPLC) and microbiological quality (Ph. Eur.).

The FP specifications have been updated during the procedures and now include specific tests required in the relevant guidelines and the Ph. Eur. Monograph for the dosage form. Impurities limits are in line with ICH Q3B. The proposed tests and limits are considered acceptable.

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. It could be shown that the risk of a carry-over of elemental impurities is very low. The concentration of all elemental impurities is far below the 30% threshold of the permitted daily intake according to ICH Q3D. Thus it has been concluded that no additional controls are required in the finished product specification.

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

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented. The finished product is released on the market based on the above release specifications through traditional finished product release testing.

Batch analysis data have been provided on three commercial scale batches manufactured by the proposed manufacturers. All the test results were within the proposed specification limits demonstrating 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 eight commercial scale batches stored for up to 60 months under long term conditions (25 ºC / 60% RH) and intermediate conditions (30°C / 65% RH) and for up to six months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The stability batches are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, assay, impurities and dissolution, for all batches at all time points. In three of those baches hardness and disintegration were also tested. The analytical procedures used are stability indicating. The analytical methods used were the same as for release and are stability indicating. The results met the specifications valid at the time.

A photostability study was conducted in accordance with ICH Q1B on one commercial scale batch. All results of appearance, assay and impurities are within specifications, no impurities have been detected, therefore the FP is considered to be photostable.

One batch of the product was stored as bulk (coated tablets prior to blistering) in the flat bags made of high-density polyethylene, the container described in Section 3.2.P.7, at 25°C/60% RH for a period of 36 months. All results are within specifications. Based on these results, it has been established that bulk coated tablets may be kept in flat bags made of high-density polyethylene for a maximum period of 36 months prior to blistering.

Based on the available stability data, the proposed shelf-life of 5 years without any special storage conditions, as stated in the SmPC (section 6.3 and 6.4) is acceptable.

2.2.3.5. Adventitious agents

Lactose monohydrate is the only material of animal origin used for Thalidomide Lipomed. 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.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance (AS) and the finished product (FP) has been presented in a satisfactory manner. The information about the active substance has been provided in the form of ASMF. A MO concerning the selection of the starting materials for the synthesis of the AS has been resolved according to the guidelines and additional information about the applied controls.

The finished product Thalidomide Lipomed 100 mg coated tablets was developed as a hybrid of Thalidomide Celgene 50mg capsules. An MO that had been raised about the development and the specification limit for the dissolution testing of the finished product has been resolved by provision of additional information and justifications and by tightening the specification limit in line with existing guidance. Another MO in relation to the *in vitro* dissolution studies in support of the bioequivalence study has been resolved by additional information as per the relevant guideline. The last MO concerned the involved manufacturing sites and the respective process validation study; this has been resolved by additional information confirming adherence to the respective guideline. Overall, during the procedure the information of the dossier has been updated and improved as requested.

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 and consistent. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

None.

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. Pharmacology

2.3.2.1. Primary pharmacodynamic studies

No new studies have been submitted. This is acceptable taking into account the type of application and that thalidomide has a well-known pharmacodynamic profile.

2.3.2.2. Secondary pharmacodynamic studies

No new studies have been submitted. This is acceptable taking into account the type of application and that thalidomide has a well-known pharmacodynamic profile.

2.3.2.3. Safety pharmacology programme

No new studies have been submitted. This is acceptable taking into account the type of application and that thalidomide has a well-known pharmacodynamic profile.

2.3.2.4. Pharmacodynamic drug interactions

No new studies have been submitted. This is acceptable taking into account the type of application and that thalidomide has a well-known pharmacodynamic profile.

2.3.3. Pharmacokinetics

No new studies have been performed. Thalidomide Lipomed is a generic/hybrid medicinal product of Thalidomide Celgene, approved through centralized procedure. The difference between products is represented by the difference in strength (50 mg for Thalidomide Celgene and 100 mg for Thalidomide Lipomed). Moreover, thalidomide is a well-known active substance with an established PK profile.

Therefore, the applicant´s approach regarding the submission of only bibliographic data publicly available is suitable and adequate.

2.3.4. Toxicology

2.3.4.1. Single dose toxicity

No new studies have been performed. The applicant´s approach regarding the submission of only bibliographic data publicly available is suitable and adequate taking into account that the toxicological profile of thalidomide is well-known.

2.3.4.2. Repeat dose toxicity

No new studies have been performed. The applicant´s approach regarding the submission of only bibliographic data publicly available is suitable and adequate taking into account that the toxicological profile of thalidomide is well-known.

2.3.4.3. Genotoxicity

No new studies have been performed. The applicant's approach regarding the submission of only bibliographic data publicly available is suitable and adequate taking into account that the toxicological profile of thalidomide is well-known.

2.3.4.4. Carcinogenicity

No new studies have been performed. The applicant's approach regarding the submission of only bibliographic data publicly available is suitable and adequate taking into account that the toxicological profile of thalidomide is well-known.

2.3.4.5. Reproductive and developmental toxicity

No new studies have been performed. The applicant´s approach regarding the submission of only bibliographic data publicly available is suitable and adequate taking into account that the toxicological profile of thalidomide is well-known.

2.3.4.6. Toxicokinetic data

No new data have been submitted.

2.3.4.7. Local Tolerance

N/A

2.3.4.8. Other toxicity studies

N/A

2.3.5. Ecotoxicity/environmental risk assessment

Thalidomide Lipomed 100 mg capsules do not represent a risk to the environment primarily due to the calculated $PEC_{SURFACEWATER}$ for thalidomide is below the 0.01 µg/l guideline threshold concentration.

In support of this statement, the applicant performed a **Phase I ERA.**

In accordance to the *Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use* (EMEA/CHMP/SWP/4447/00 Corr2), the applicant calculated $PEC_{surfacewater}$ as follows:

$$PEC_{\text{surfacewater}} = \frac{DOSE\text{ai} \; x \; F\text{pen}}{WASTEW\text{aterinhab} \; x \; DILUTION} \; x \; 1000$$

Symbol	Parameter	Value
Input		
*DOSE*ai	Maximum daily dose of active ingredient consumed per inhabitant	200 mg/inh/d
*F*pen	Fraction of market penetration	0.01
*WASTEW*aterinhab	Amount of wastewater produced per inhabitant per day	200 l/inh/d
DILUTION	Dilution factor in receiving water	10
1000	Conversion factor (mg to µg)	1000 µg/mg
Output		
$PEC_{surfacewater}$	Predicted environmental concentration in local surface water	1.000 µg/l

It is noticed that PECsurfacewater exceeds 0.01 µg/l, the accepted value in the currently used ERA guidance. Therefore, the applicant refined Fpen based on prevalence data and treatment regimen, in accordance to Q&A on the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/44609/2010, Rev.1).

$$F\text{pen} = \frac{CON\text{ai}_{\text{region}}}{DOSE\text{ai} \; x \; n_{\text{i,region}} \; x \; N_{\text{d}}} = \frac{DOSE\text{ai} \; x \; t_{\text{treatment}} \; x \; n_{\text{treatment,p}} \; x \; P_{\text{region}} \; x \; n_{\text{i,region}}}{DOSE\text{ai} \; x \; n_{\text{i,region}} \; x \; N_{\text{d}}} = P_{\text{region}} \; x \; \frac{t_{\text{treatment}} \; x \; n_{\text{treatment,p}}}{N_{\text{d}}}$$

The determined value of PECsurfacewater based on the formula mentioned in the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00, Corr 2) is PECsurfacewater= 0.0000313 x 200/200 X10 X 1000. Therefore, the determined value of 0.0031 µg/L is well below the value stipulated in the currently used ERA guideline, respectively 0,01 µg/l.

2.3.6. Discussion on non-clinical aspects

The non-clinical overview is based on published literature data. This is acceptable since thalidomide is well known active substance and with extensive experience in clinical setting. There are no new non clinical studies performed in support of the proposed application hence the presented Non-clinical Overview is considered sufficient for this type of MAA. No issue has been raised regarding the impurities and residual solvents found in drug substance/drug product from toxicological point of view.

Section 4.6 (Fertility, Pregnancy and Lactation) and the Preclinical safety data (section 5.3) contained in the proposed SmPC for Thalidomide Lipomed reflects the characteristics of the substances and are completely in line with the reference medicinal product Thalidomide Celgene approved through centralized procedure (EMEA/H/C/000823).

The applicant performed a Phase I ERA and provided supplementary PK data, taking into account that thalidomide is a known human teratogen. These data support the fact that Thalidomide Lipomed is unlikely to represent a risk for the environment following its prescribed usage in elderly patients with multiple myeloma. Two queries have been identified at Day 120. In the ERA assessment the prevalence data initially presented were not accurate. The applicant was referring to new cases in 2018 but when accessing the links (facts-sheets) below the table then numbers given seem to be from 2020. As requested, the applicant provided adequate data. It can be considered that this question is considered solved. Initially, logK_{ow} has been provided based on the scientific literature publicly available. Following the assessment question, the applicant provided suitable and reliable information on an experimentally derived n-octanol/water partition coefficient (log K_{ow}) for the active ingredient in order to assess the PBT potential, in accordance with the Q&A document by the European Medicines Agency (EMA) Questions and answers on 'Guideline on the environmental risk assessment of medicinal products for human use' (EMA/CHMP/SWP/44609/2010)**.**

2.3.7. Conclusion on the non-clinical aspects

The non-clinical information provided is considered adequate to support the approval.

2.4. Clinical aspects

2.4.1. Introduction

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

GCP aspects

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

Table 1. Tabular overview of clinical studies

Type of Study	Study Identifier	Location of the study report	Objective of the study	Study design and type of control	Test Product; dosage regimen; route of administration	Number of subjects	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; type of report
Comparative BA/BE	1386tha20ct	Module 5.3.1.2	Bioequivalence of one 100 mg coated tablet of Test in comparison to two 50 mg hard capsules of Reference; Characterisation of relevant pharmacokinetic parameters; Descriptive characterisation of safety and tolerability	Single centre, open-label, randomised (order of treatments), balanced, 2-period, 2-sequence, single dose cross-over trial; fasted administration	Thalidomide Lipomed 100 mg coated tablets; 1 tablet of 100 mg, single dose administration; oral	34	Healthy subjects	Single dose	Complete; full

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

Study Protocol Number 1386tha20ct:

Characterisation of relative bioavailability of a newly developed thalidomide formulation (100 mg) in comparison with a marketed reference product (2x50 mg)

Methods

- **Study design**

This was a single centre, open-label, randomised, balanced, 2-period, 2-sequence-crossover, single dose trial in healthy adult volunteers under fasting conditions.

Duration of the study:

Study initiation date (first subject enrolled): 09.07.2020

Study completion date ((last subject completed): 18.08.2020

Washout period: at least 03 days between dosing of each period

Subjects enrolled in the study were dosed on the following dates:

Period 1: on 20.07.2020 subjects 001 – 017 and on 23.07.2020 subjects 018 - 034

Period 2: on 26.07.2020 subjects 001 – 017 and on 29.07.2020 subjects 018 – 034

Site and dates of the study

Approval of the IEC and BfarM of the study protocol, amendment 02, final of the study protocol dated 02.07.2020 and approval of the Informed Consent (Version Number V01, final) by the have been provided as requested at Day 120.

The final clinical study report is dated 28.01.2021.

The treatments were defined as follows:

T: single oral fasted administration of 1 coated tablet of Test (Thalidomide Lipomed 100 mg coated tablet manufactured by Lipomed GmbH, Germany.

R: single oral fasted administration of 2 hard capsules of Reference (Thalidomide Celgene 50 mg hard capsule MAH Celgene Europe B.V., Netherlands. taken simultaneously

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

SEQUENCE	**No. of subjects**	**Period I**	**Period II**
Sequence 1 (RT)	17	Reference	Test
Sequence 2 (TR)	17	Test	Reference

After an overnight fast of at least 8 hours, subjects were administered orally either two hard capsules of Thalidomide Celgene (Reference) or one coated tablet of Thalidomide Lipomed (Test) as per randomisation schedule. The hard capsules and tablets were administered with 240 ml tap water in an upright position.

Standardised meals were provided in the evening of pre-administration day (i.e. study day -1) and on the day of administration of the IMP subjects received standardised meals 4, 7, 9 and 12 hours after dosing in each period. Water was restricted from 01 hour prior to dosing until 01 hour post-dose,

except 240 ml tap water given during dosing. From 01 hour until 10 hours after dosing 150 ml of non-carbonated water were given every hour, i.e. 150 ml were given ten times. After this interval fluid intake of non-carbonated water was ad libitum.

The design of the study is in line with the requirements of the *Guideline on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 01 – January 2010); therefore, it is considered appropriate.

The test and the reference products are immediate release formulation; thus, a single dose bioequivalence study is appropriate.

According to the SmPC the reference product should be taken as a single dose at bedtime due to sedative effects. While absorption is delayed in fed state the overall extent of absorption is not altered. Thus, the bioequivalence study conducted under fasting conditions is acceptable.

The blood sampling for the assessment of thalidomide in plasma were collected pre-dose (within 1.0 hour prior to dosing) and post-dose at 0.25, 0.5, 0.75, 1, 1.33, 1.66, 2, 2.33, 2.66, 3, 3.33, 3.66, 4, 4.5, 5, 5.5, 6, 8, 10, 12, 18, 24, 36 and 48 hours. Frequent sampling was planned around the expected t_{max} (1-5 hours).

Considering the median t_{max} at 2 hours post-dose, the sampling period and the sampling scheme seems adequate to estimate the primary PK parameters of thalidomide.

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

The mean apparent terminal $t_{1/2}$ following a 100 mg oral dose of thalidomide was approximately 5.70 hours, thus the washout period of at least 03 days is more than five half-life of the active substance. This is considered appropriate to exclude a carry-over effect.

Table 2. Test and reference products

TT 2: Pharmaceutical information on Test and Reference product

Pharmaceutical information	Test product	Reference product
Product name	Myrin® 100 mg	Thalidomide Celgene®
Manufacturer / MA Holder	Lipomed GmbH (batch release)	Celgene Distribution B.V. / Celgene Europe B.V.
Member state where the reference product is purchased from	-	Germany
Dosage form	Coated tablet	Hard capsule
Active ingredient	Thalidomide	Thalidomide
Strength	100 mg	50 mg
Batch No.	1017371	E2025P3
Expiry date/use-by date	04/2022	03/2022
Excipients	Tablet core: Lactose monohydrate Copovidone Talc Magnesium stearate Microcrystalline cellulose Tablet coating: Heavy kaolin Sucrose Acacia Calcium carbonate Talc Titanium dioxide	Capsule contents: Starch, pregelatinized Magnesium stearate Capsule shell: Gelatin Titanium dioxide (E171) Printing ink: Shellac Black iron oxide (E172) Propylene glycol
Storage conditions	Do not store above 25°C	Do not store above 25°C
Marketing authorisation number	-	EU/1/08/443/001
Manufacturing date	April 2019	-
Batch size (Biobatch)	289,000 coated tablets	-
Commercial batch size	200,000 – 600,000 coated tablets	-
Assay [%]	101.7	97.2

The reference product Thalidomide Celgene is approved in the European Union. Samples originated from normal production batches. The choice of the reference product is appropriate.

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

- **Population(s) studied**

A total of 40 healthy, adult, male subjects have been enrolled in the clinical trial, from which 34 have been randomised (Caucasian race, mean age 36.6±10.4 years, mean height 1.815±0.069 m, mean weight 84.40±11.67 kg, mean BMI 25.53±2.47 kg/m2). All randomised subjects were non-smokers or ex-smokers since at least 6 months. The study population was chosen according to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 01 – January 2010). As thalidomide has teratogenic potential, only male subjects have been included in the bioequivalence study, which is agreed.

All the subjects enrolled in the study fulfilled the inclusion and exclusion criteria. All the subjects were of normal health based on the general physical examination and laboratory tests. None of the subjects had any relevant or significant previous medical history that could affect the study results.

The number of the subjects included was based on an adequate sample size calculation and is found sufficient.

From 34 subjects randomised, 34 subjects completed the study. 33 have been included in the PK and statistical analyses. The individual values for the PK parameters determined for subject 016 have been reported but not included in the statistical analysis in line with the pre-specified criteria in the protocol.

Two major protocol deviations on clinical part were reported, i.e. work up of plasma and interruption of upright position, both for the same subject 016; these deviations have been considered by the applicant to have the potential to affect the PK parameters. The subjects with major protocol deviations are excluded from the per-protocol analysis and that was pre-specified in the protocol. Thus, concentration data and pharmacokinetic parameters from dropped out or excluded subjects will be presented in the individual listings, if available, but will not be included in the summary statistics. According to the protocol, the bioequivalence assessment has been based on the results calculated without the data of the excluded subjects.

As long as the strict restrictions on public life due to COVID-19 pandemic were in place, the trial was conducted in 2 groups in order to reduce the physical contact of individual persons to an absolutely necessary minimum allowing single room accommodation of the subjects.

According to the protocol no subgroup analysis is planned. The study protocol has not been amended to specify that the subjects to be enrolled and dosed have to be divided into two dosing groups. The clinical study takes place at one site. The interval between groups is 3 days.

- **Analytical methods**

Short description of the analytical method

The plasma samples of subjects have been analysed using a validated analytical method.

Blood samples were collected in into K2EDTA tubes and centrifuged within 30 min (centrifugation conditions: 2000 x g, 10 min, 4ºC) to separate plasma. The stability of Thalidomide in whole blood for 30 minutes after the blood samples have been drawn and before their centrifugation has been established in an ice bath, as requested at Day 120. Issue is resolved.

The plasma samples were frozen and retained at ≤ -20ºC until analysed. The bioanalyses were carried out between 26.08.2020 and 18.09.2020.

- **Pharmacokinetic Variables**

Computation of the following pharmacokinetic variables has been performed: Cmax, AUC0-tlast, AUC0-∞, AUCextrapol%, Tmax, Tlast, Tlag, T1/2, and Lz (= λ) for Thalidomide Lipomed (Test product) and Thalidomide Celgene (Reference Product).

The primary pharmacokinetic parameters are: AUC0-tlast and Cmax.

The secondary pharmacokinetic parameters are: AUC0-∞, AUCextrapol%, Tmax, Tlast, Tlag, T1/2 and λ.

Pharmacokinetic parameters have been calculated from individual plasma concentrations of 33 subjects out of 34 enrolled who completed both periods of the clinical trial successfully.

The pharmacokinetic parameters are adequate for a bioequivalence trial with immediate-release formulations.

Subject 016 was excluded from the statistical analysis due to major protocol deviations, one considered to potentially affect Cmax and another to potentially interfere with the absorption process. In the responses provided at Day 121, the applicant submitted a full statistical and pharmacokinetic analysis with all 36 subjects included. The issue was solved.

- **Statistical methods**

Statistical analysis was performed on ln-transformed pharmacokinetic parameters.

Descriptive statistics (N, arithmetic means, SD, geometric means, geometric CV, medians, minimum, and maximum) were presented for all pharmacokinetic parameters, separately for each treatment.

In cases of missing value for a pharmacokinetic metric, this value has been reported as missing. For pairwise comparisons also the value to be compared has been considered missing, i.e. has been excluded from the comparison. However, this value remain in descriptive statistics, if the subject was considered eligible.

Analysis included the factors formulation, period, sequence and subject(sequence) as fixed effects. Intra-subject variability was estimated and period, subject and sequence effects were determined.

Affiliated statistical analyses were performed with an error probability of 0.05 (type-I error probability).

Parametric point and interval estimates of Test/Reference ratio were calculated for AUC- and C_{max}–values.

Relative bioavailability of Test vs. Reference was assessed by the ratios of geometric last square means (point estimates). This was computed and reported for Ln-transformed pharmacokinetic parameters $AUC_{0\text{-}tlast}$ and C_{max}.

90% confidence intervals served as interval estimates and were determined by parametric analysis (two one-sided t-tests).

As the subjects were enrolled and dosed divided in two groups 3 days apart, the group effect should be included in the ANOVA model and a new statistical analysis should be performed or otherwise it should be further justified. As requested, at Day 121, an additional statistical evaluation of the pharmacokinetic values of study 1386tha20ct was performed. Treatment comparison was performed by new ANOVA model considering group as an additional effect in analogy to the procedure of the initial evaluation described in the Statistical Analysis Plan.

Analysis included the factors formulation, group, period(group), sequence, sequence*group and subject (sequence*group) as fixed effects.

The inclusion of the factor Group in the ANOVA model was based on the analogue evaluation of the factor Stage in the ANOVA model as recommended by EMA for the two-stage bioequivalence study design (ANOVA factors according to the point 3.2 from EMA “Clinical pharmacology and pharmacokinetics: questions and answers”)

In order to evaluate correctly the significance of the effects, the applicant conducted an ANOVA with the factor subject(sequence*group) as random effect in addition to the ANOVA with the factor subject(sequence*group) set as fixed effect.

The inference from the treatment comparison was found identical in both approaches.

The group effect was not found statistically significant for any PK parameters by using ANOVA model with the factor subject(sequence*group) as random effect.

Intra-subject variability was estimated and the aforementioned effects were determined.

Affiliated statistical analyses were performed with an error probability of 0.05 (type-I error probability). Parametric point and interval estimates of Test/Reference ratio were calculated for AUC0-inf-, AUC0-tlast- and Cmax–values.

Relative bioavailability of Test vs. Reference was assessed by the ratios of geometric means (point estimates). 90% confidence intervals served as interval estimates and were determined by parametric analysis (two one-sided t-tests).

Criteria for conclusion of bioequivalence

The acceptance criteria for bioequivalence were that the entire confidence intervals for the difference of means of Ln-transformed $AUC_{0\text{-}tlast}$ and C_{max} should be within 80.00% -125.00%.

Results:

Table 3. Pharmacokinetic parameters for Thalidomide (non-transformed values)

Pharmacokinetic parameter	**Test**		**Reference**	
	arithmetic mean geometric mean	**SD CV%**	**arithmetic mean geometric mean**	**SD CV%**
$AUC_{(0\text{-}tlast)}$ (h*ng/mL)	**10400** 10300	**1370** 13.35%	**10100** 10000	**1410** 14.04%
$AUC_{(0\text{-}\infty)}$ (h*ng/mL)	**10400** 10300	**1380** 13.39%	**10100** 10000	**1430** 14.16%
C_{max} (ng/mL)	**1270** 1250	**218** 17.45%	**1030** 1010	**189** 20.08%
T_{max}* (h)	**2.00 (0.500 – 3.66)**	0.861	**2.66 (0.750 – 8.00)**	1.26
$AUC_{0\text{-}tlast}$ area under the plasma concentration-time curve from time zero to the last measurement time point with a concentration value above the lower limit of quantitation				
$AUC_{0\text{-}\infty}$ area under the plasma concentration-time curve from time zero to infinity				
C_{max} maximum plasma concentration				
T_{max} time for maximum concentration (* median, range)				

Table 4. Statistical analysis for Thalidomide (ln-transformed values)

Pharmacokinetic parameter	**Geometric Mean Ratio Test/Reference**	**Confidence Intervals**	**CV%***
$AUC_{(0\text{-}tlast)}$	103.32	102.01 – 104.63	3.03%

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
C_{max}	124.09	116.31 – 132.39	15.60%
* estimated from the Residual Mean Squares			

Figure 2. Mean plasma concentration vs. time curves of thalidomide after oral single dose administration of 1 tablet of Myrin® 100 mg (Test) and 2 hard capsules of Thalidomide Celgene® (Reference) under fasting conditions to 33 subjects (100 mg thalidomide per treatment)

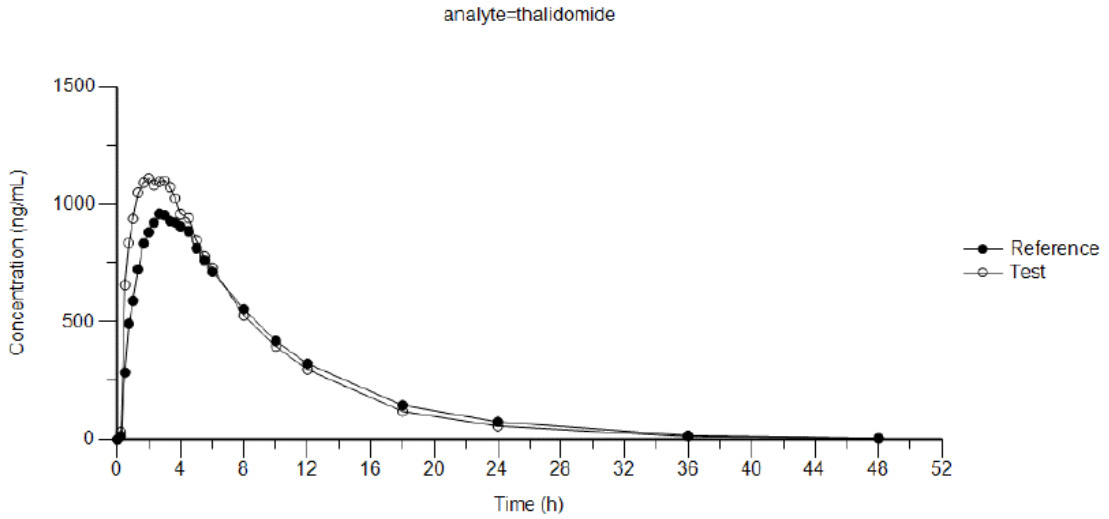

Figure 3. Mean plasma concentration vs. time curves of thalidomide after oral single dose administration of 1 tablet of Myrin® 100 mg (Test) and 2 hard capsules of Thalidomide Celgene® (Reference) under fasting conditions to 33 subjects (100 mg thalidomide per treatment), semi – logarithmic plot.

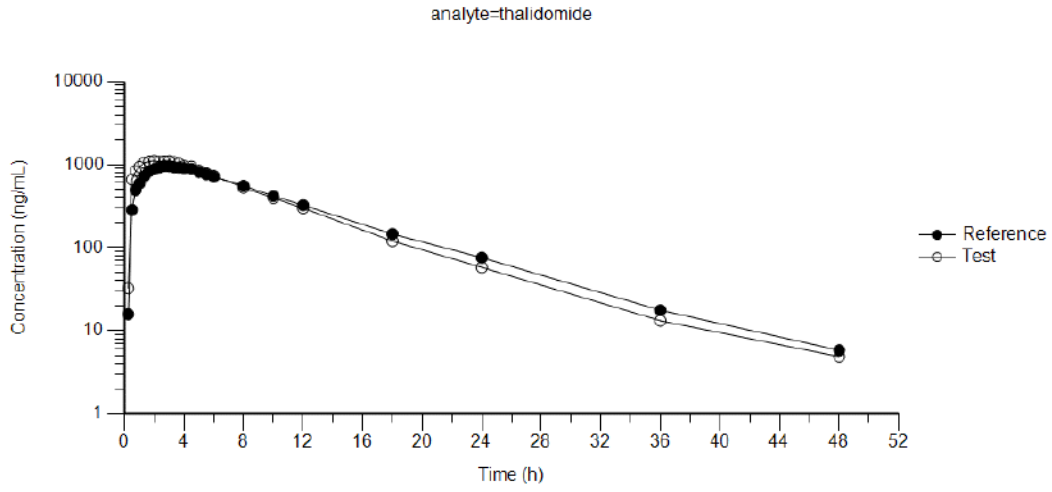

Table 5. ANOVA Summary Table

Parameters	**ANOVA p-values**	
Effects	**C_{max}**	**$AUC_{0\text{-}tlast}$**
Sequence	0.5089	0.8148
Treatment	0.0000	0.0001
Period	0.2449	0.3335
Sequence(subject)	0.0364	0.0000

The statistical evaluation (CI and PE) including subject 016 was provided as requested:

Table 6. Parametric point estimates and 90 % confidence intervals determined for pharmacokinetic parameters of thalidomide; comparison of Test vs. Reference

Parameter	Observations	Point Estimate	90% confidence interval		CV_{ANOVA}
			Lower Limit CI	Upper Limit CI	
$AUC_{0\text{-}tlast}$	68	103.35	102.09	104.63	2.99
$AUC_{0\text{-}inf}$	68	103.19	101.91	104.48	3.03
C_{max}	68	124.90	117.20	133.10	15.58

Inclusion of subject 016 did not affect the statistical comparison of AUC0-tlast or AUC0-inf as point estimate and confidence interval for both parameters remained nearly identical compared to the previous evaluation without subject 016.

For Cmax the point estimate also remained nearly identical, the confidence interval did slightly change with a minor trend to higher values (116.31 - 132.39 % without subject 016 to 117.20 – 133.10 % with subject 016).

In response to Day 120 request the confidence intervals for the PK primary parameters were also calculated using ANOVA model with the "group" as an additional effect.

Table 7. CI and Residual Variances of the primary pharmacokinetic parameters (N=34 subjects)

Parameter	Obser-vations	Effect	Test	Reference	PE	Lower Limit CI	Upper Limit CI	CV	Residual Variance
$AUC_{0\text{-}inf}$	68	treatment	Test	Reference	103.19	101.89	104.51	3.08	0.00094759449
$AUC_{0\text{-}tlast}$	68	treatment	Test	Reference	103.35	102.07	104.65	3.04	0.00092206429
C_{max}	68	treatment	Test	Reference	124.34	117.03	132.11	14.79	0.021648069

in comparison with the initial results:

Table 8. CI and Residual Variances of the primary pharmacokinetic parameters (N=33 subjects)

Parameter	Obser-vations	Effect	Test	Reference	PE	Lower Limit CI	Upper Limit CI	CV	Residual Variance
$AUC_{0\text{-}inf}$	66	treatment	Test	Reference	103.15	101.84	104.49	3.08	0.0009459395
$AUC_{0\text{-}tlast}$	66	treatment	Test	Reference	103.32	102.01	104.63	3.03	0.00092061797
C_{max}	66	treatment	Test	Reference	124.09	116.31	132.39	15.6	0.024041923

The results indicated no significant effect for any of the primary pharmacokinetic parameters in comparison with the initial results, therefore the applicant considered pooling the data of both groups justified.

The Group-by-Formulation interaction was not included in the new ANOVA model and this effect should be tested. The applicant is asked to provide the statistical analysis with an updated ANOVA model including the Group-by-Formulation interaction effect in the statistical model.

As requested, the exploratory analysis conducted separately by each group using the ANOVA model updated with the group by treatment interaction has been provided. Consistently with results obtained with the initial ANOVA analysis, the equivalence of Test and Reference was demonstrated in respect to the primary pharmacokinetic parameter AUC0-tlast but not for Cmax. The applicant provided a clarification regarding the number of observations mentioned in the table results for each group. Issue solved.

- **Safety data**

Safety parameters have been assessed in all 34 randomised subjects (FAS) throughout the study till completion. None of the subjects dropped out due to AEs.

During the study, 23 AEs (56.10%) have been reported in 19 subjects (55.88%) after Test product administration and 18 AEs (43.90%) in 12 subjects (35.29%) after Reference product administration.

32 out of 41 AEs (78.05 %) reported were assessed as study drug related and 9 out of 41 (21.95 %) as with no causal relationship. Eighteen (18) out of 32 (56.25 %) of the study drug related AEs were reported after Test treatment and 14 out of 32 (43.75 %) after Reference.

The intensity of all AEs was mild in 29 out of 41 cases (70.73%) and moderate in 12 out of 41 cases (29.27%) and in no case severe.

In case of study drug related AEs, the intensity was mild in 20 out of 41 cases (48.78 %) and moderate in 12 out of 41 cases (29.27%).

Of the mild and drug related AEs, 11 could be associated to the Test and 9 to the Reference product. Drug related AEs of moderate intensity could be assigned to Test in 7 cases and to Reference in 5 cases.

There were no subjects who reported long-term medication during the study.

There were no serious AEs and no deaths reported in the BE study.

Overall, the AEs reported in the BE study are in line with the known safety profile of thalidomide. There were no apparent differences in safety profiles, except fatigue, which was reported slightly more in subjects after Test product administration than after Reference product administration.

No clinically relevant changes in the ECG parameters, vital signs and physical parameters related to safety were observed during the study.

2.4.2.2. Pharmacokinetic conclusion

The 90% confidence interval for the ln-transformed values for AUC0-tlast was within the 80.00-125.00% limit and is considered acceptable. In respect to the primary endpoint, AUC0-tlast, the bioequivalence was demonstrated. However, it should be noted that the confidence interval does not contain unity.

The 90% confidence interval for the ln-transformed values for Cmax was not contained within the 80.00- 125.00% limit, as the upper limit of the confidence interval was above 125%. Thus, in respect to the primary endpoint Cmax bioequivalence was not demonstrated.

2.4.2.3. Pharmacodynamics

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

2.4.3. Clinical safety

2.4.3.1. Post marketing experience

According to the applicant, Thalidomide Lipomed 100 mg, under the name Myrin 100 mg, is not a new formulation and it is authorised in three third countries: Ukraine, Morocco and Macedonia. In addition, in Ukraine and Morocco another strength, 50 mg, is authorised. The international birth date (IBD) for Myrin of Lipomed AG is the 18.05.2006. The authorised indication of Myrin 50 and Myrin 100 is multiple myeloma after failure of standard therapies.

Moreover, the product Myrin has been also distributed under national specific programs in several countries worldwide since IBD: Albania, Austria, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Egypt, Great Britain, Hungary, Islamic Republic of Iran, Iraq, Jordan, Kuwait, Lebanon, Lithuania, Montenegro, Mexico, Montenegro, Oman, Poland, Romania, Russia, Saudi Arabia, Serbia, Slovakia, Slovenia, South Africa, State of Palestine, Syria, Switzerland, Togo, Tunisia, Yemen, Vietnam, The Bahamas, Curacao, Barbados, Saint Kitts, Jamaica.

Prior to marketing authorisation in the respective country, Myrin has also been distributed under the terms of national specific programs in Macedonia and Morocco.

Since market introduction of Myrin 50 and Myrin 100, 155 spontaneous serious ADRs, 765 spontaneous non-serious ADRs and 3 serious ADRs from non-interventional post-marketing studies or from reports from other solicited sources, respectively, were received by the MAH.

No data concerning ADRs by strength was provided by the MAH. The MAH was requested to provide a separate line-listing of cases serious/non-serious ADRs for from post-marketing sources received cumulatively for each strength of the product (presented by SOC/PT). The issue was solved

Cumulatively, the most reported PTs are the following: neuropathy peripheral (131 ADRs), anaemia (102 ADRs), thrombocytopenia (98 ADRs), neutropenia (95 ADRs), infection (73 ADRs), fatigue (77 ADRs), vomiting (48 ADRs), constipation (50 ADRs), pain (29 ADRs), rash (21 ADRs), peripheral swelling (13 ADRs), diarrhoea (25 ADRs).

The pattern of distribution of the most frequently reported ADRs remains in general consistent with the known safety profile of thalidomide.

Having considered the data exposed in the last PSUR, we agree that the medicinal product has an acceptable safety profile. No new safety concerns have been identified. In addition, as requested at Day 120, the risk of medication errors was added in the Summary of safety concerns.

2.4.1. Discussion on clinical aspects

To support this art. 10(3) application, change in the strength as compared to the Reference product, the company submitted one bioequivalence study and literature data on clinical pharmacology, efficacy and safety. The demonstration of bioequivalence by conducting a relative bioavailability study comparing one coated tablet of Thalidomide Lipomed 100 mg to two hard capsules of Thalidomide Celgene 50 mg (reference medicinal product) was recommended by the CHMP, in order to support this article 10(3,) so-called 'hybrid', application of Thalidomide Lipomed 100 mg coated tablet. The applicant has not submitted any other clinical studies to support this application. As the new strength is covered by the posology of the Reference product, this can be considered acceptable, provided that the bioequivalence criteria are fulfilled.

The bioequivalence study with protocol 1386tha20ct was a single centre, open-label, randomised, balanced, 2-period, 2-sequence-crossover, single dose trial in healthy adult volunteers under fasting conditions between 100 mg coated tablet of Thalidomide Lipomed (by Lipomed GmbH) in comparison to two 50 mg hard capsules of Thalidomide Celgene (by Celgene Europe B.V.). The Marketing authorisation of Thalidomide Celgene has been transferred to another MAH, and it is currently known as Thalidomide BMS.

The applicant has stated that the study has been conducted in compliance with GCP and GLP requirements. The bioequivalence study has been conducted at a CRO, which according to the applicant was subject to a GCP inspection in 2019 by the Authority of the state Thuringia, Germany. In addition, the applicant mentioned that a GCP inspection of the sponsor in Germany, has been conducted by the Authority of the state Hesse, Germany in 2018. At Day 121, the applicant submitted statements concerning the outcome of GCP inspections performed by EU authorities at the CRO, clinical and analytical sites. These statements are signed by the CRO and according to them no critical findings have been found by the EU authorities which inspected the clinical trial facilities. No inspection reports have been provided and no inspection for study 1386tha20ct was performed. As no potential major or critical findings relevant for the actual study were identified the issue is considered solved.

The applicant was requested to provide quality assurance documents and monitoring reports of study 1386tha20ct performed, according to the *Guidance on the management of clinical trials during COVID-19 pandemic*, as these have not been found in the dossier. The applicant clarified that no specific audit have been performed during the study, therefore no quality assurance documents are available. However, the applicant mentioned that study-specific auditing of trial activities has been performed for other studies running in parallel and additional system audits have been performed, and as a consequence, each study benefits from quality improvement of processes even if no study-specific audit activity is performed as this was the case for Study 1386tha20ct. In the *EMA/HMA Guidance on the management of clinical trials during the COVID-19 pandemic*, it is mentioned that "*in the current situation, on-site audits should, in general, be avoided or postponed*" and "*can be considered, after the*

agreement with the investigator and if audits are assessed as essential, e.g. triggered audits with the purpose of investigating serious deviations from the trial protocol or from applicable legislation". During the assessment no GCP issues arose, therefore, the issue was not pursued further. The monitoring reports have been submitted as requested.

According to the applicant, BfArM and an Independent Ethics Committee reviewed the protocol and the amendments to the protocol and the Informed Consent Form (ICF) was reviewed by the Independent Ethics Committee; the study was initiated after the approval from the IEC and BfArM. As requested, the approvals from the IEC and BfArM have been provided.

According to the SmPC, the reference product should be taken as a single dose at bedtime *with or without food*, thus the bioequivalence study conducted under fasting conditions is acceptable.

The selection of the highest dose, 100 mg, to be used in the bioequivalence study under fasting conditions is justified and in accordance with the guidelines.

Overall, the study design is acceptable and in line with the pharmacokinetic properties of Thalidomide.

The sampling period was sufficient, the sampling schedule and wash-out period were adequate taking into account the t_{max} and apparent terminal $t_{1/2}$. Since AUC_{0-t} covers at least 80% of $AUC_{0-\infty}$, the sampling schedule covers the plasma concentration time curve long enough.

The population was chosen according to the guidelines. 34 subjects were randomised and completed the study. 33 were included in the PK and statistical analyses.

Bioanalytical method had satisfactory performance and was adequately validated. The pharmacokinetic and statistical methods applied were appropriate for a single-dose study.

Cmax was not observed in any subject at the first time point and pre-dose concentration has not been detected in any subject. The extrapolated AUC was not higher than 20% in any subject, thus the blood-sampling schedule up to 48h was defined adequately.

Maximum exposure was higher for the Test product (arithmetic mean 1270 ng/mL) compared to the Reference product (arithmetic mean 1030 ng/mL). The median value of time to reach maximum exposure was slightly lower for Test product (2.00 h) as compared to Reference product (2.66 h). This indicate that the rate of thalidomide absorption from Test is higher as compared to Reference.

For $AUC_{0-tlast}$ and C_{max} parameters a statistically significant sequence or period effect was not shown, as the p values were above 0.05. For both $AUC_{0-tlast}$ and C_{max} parameters a statistically significant treatment effect was shown. The detected statistically significant treatment effects are expected as the lower bound of the 90% CI is above 100% for both $AUC_{0-tlast}$ and C_{max} parameters, indicating that there is a treatment effect, and the two products are not identical in terms of AUC or C_{max}. They may still be considered bioequivalent, provided that the CI is contained within the usual boundaries.

However, the 90% confidence intervals for the ratio of the ln-transformed values test and reference products are within the acceptance range of 80.00 - 125.00% only for $AUC_{0-tlast}$.

At Day 120, a major objection on the lack of the demonstration of the BE was identified. The 90% CI for the Cmax partially overlaps the acceptance range having the upper limit 132.39% and therefore exceeds the required limit of 125.00.

An issue was identified regarding the exclusion of one subject (016) from the statistical and pharmacokinetic analysis. As requested, the applicant submitted a full statistical and pharmacokinetic analysis with all 36 subjects included. After inclusion of Subject 016, the point estimates and the confidence intervals for AUC_{0-last} and AUC_{0-inf} were nearly identical compared to those obtained after statistical and pharmacokinetic analysis of 35 subjects. The point estimate for C_{max} also remained

nearly identical. The confidence interval was slightly changed, i.e. 116.31 - 132.39 % without subject No. 016 and 117.20 – 133.10 % with subject 016.

As the subjects were enrolled and dosed divided in two groups 3 days apart, as requested, an additional statistical evaluation of the pharmacokinetic values of study 1386tha20ct was performed.

Treatment comparison was performed by new ANOVA model considering group as an additional effect in analogy to the procedure of the initial evaluation described in the Statistical Analysis Plan.

Analysis included the factors formulation, group, period(group), sequence, sequence*group and subject (sequence*group) as fixed effects.

The inclusion of the factor Group in the ANOVA model was based on the analogue evaluation of the factor Stage in the ANOVA model as recommended by EMA for the two-stage bioequivalence study design (ANOVA factors according to the point 3.2 from EMA "*Clinical pharmacology and pharmacokinetics: questions and answers*")

In order to evaluate correctly the significance of the effects, the applicant conducted an ANOVA with the factor subject(sequence*group) as random effect in addition to the ANOVA with the factor subject(sequence*group) set as fixed effect.

The inference from the treatment comparison was found identical in both approaches.

The group effect was not found statistically significant for any PK parameters by using ANOVA model ANOVA with the factor subject(sequence*group) as random effect.

In response to the request, the confidence intervals for the PK primary parameters were also calculated using ANOVA model with the "group" as an additional effect. The results indicated no significant effect for any of the primary pharmacokinetic parameters in comparison with the initial results, therefore the applicant considered justified pooling the data of both groups.

The exploratory analysis conducted separately by each group using the ANOVA model updated with the group by treatment interaction has been provided as requested. Consistently with results obtained with the initial ANOVA analysis, the equivalence of Test and Reference was demonstrated in respect to the primary pharmacokinetic parameter $AUC_{0\text{-}tlast}$ but not for C_{max}.

The observed variability for C_{max} was 15.60%, much lower that the assumed value of 25% taken into account in the sample size calculation; in addition, the drop-out rate was lower than anticipated. The minimum number of subjects required to establish the bioequivalence was estimated at 28 subjects.

Despite the fact that the Cmax values of the applied hybrid medicinal product is approximately 24% higher than that of the reference product, a similar exposure was achieved as the AUC test/reference ratio was contained in the BE range. In the conducted relative bioavailability study, Cmax of the Test product was achieved faster than the Cmax of the Reference product, i.e. 2.00 (0.50 – 3.66) hours as comparedwith 2.66 (0.75 – 8.00) hours. From the data published, it appears that absorption of thalidomide is dependent on its solubility in gastric fluid, which is dependent on its dissolution rate in the gastrointestinal tract. Once the gastric fluid at the absorption site has been saturated with drug, further dissolution may not take place until some of the drug is absorbed across the intestinal lumen. The low solubility of thalidomide in the gastrointestinal tract results in a "flip-flop" phenomenon. That means, that the rate of absorption is significantly slower than the rate of elimination from the body.

C_{max} could give rise to adverse events. The incidence and severity of adverse events are related to dose and duration of therapy.

The EPAR of Thalidomide Celgene (currently known as Thalidomide BMS) mentions that thalidomide has a narrow safety margin (100 – 400 mg) and the tolerability was better at the 200 mg/day dose as

compared to 400 mg/day. The risk of toxic ADRs increases in a dose-dependent manner. As such, the recommended dose in the reference product SmPC is 200 mg thalidomide orally per day administered for a limited period of time, i.e. maximum number of 12 cycles of 6 weeks (42 days). In section 4.2 Posolgy and method of administration, it is written that "patients should be monitored for: thromboembolic events, peripheral neuropathy, severe skin reactions, bradycardia, syncope, somnolence, neutropenia and thrombocytopenia. Dose delay, reduction or discontinuation, dependent upon the NCI CTC (National Cancer Institute Common Toxicity Criteria) grade, may be necessary". Peripheral neuropathy is a very common, potentially severe, adverse reaction that may result in irreversible damage. It general occurs after chronic use; however, reports following relatively short-term use also exist. Incidence of neuropathy events leading to discontinuation, dose reduction or interruption increases with cumulative dose and duration of therapy. Grade 1-2 NCI CTC peripheral neuropathy can occur in more than 80% of patients, whereas severe grade 3-4 neuropathy occurs in approx. 3-5% of patients.

Because the occurrence of peripheral neuropathy is not predictable and a preventive treatment does not exist, minimisation measures are important, such as those mentioned in the SmPC, i.e. dose delay, reduction or discontinuation, dependent upon the NCI CTC grade.

To demonstrate that the differences in Cmax between the Test (one Thalidomide Lipomed 100 mg coated tablet) and Reference (two Thalidomide Celgene 50 mg hard capsules) formulations of thalidomide at the recommended therapeutic dose of 200 mg are clinically not relevant, the Cmax value observed for Test in the relative bioavailability study 1386tha20ct was dose-adjusted (extrapolated considering 15% deviation from proportionality) and compared with published thalidomide Cmax values following administration of thalidomide 200 mg.

Assuming a linear pharmacokinetics for thalidomide from Thalidomide Lipomed, mean Cmax values around 2500 ng/mL would theoretically be expected at the highest recommended dose (200 mg/day).

However, in line with the available published data related to the Thalidomide dose proportionality, a significant deviation from proportionality has been noticed for Cmax with increases being less than proportional than dose increase and almost dose proportionality for AUC0-∞. Therefore, at higher doses, the drug may be absorbed at a slower rate.

As in study 1386tha20ct, a comparison of one 100 mg coated tablet of Test (Thalidomide Lipomed 100 mg) to two 50 mg hard capsules of Reference (Thalidomide Celgene 50 mg) after single-dose administration under fasted conditions was performed, the pharmacokinetic parameters of the approved daily dose of 200 mg have not been determined. Therefore, the applicant estimated the concentration profiles for the test and reference products at steady state after multiple doses of 100 mg and 200 mg and after single dose of 200 mg based on the pop PK model.

As mentioned above, specifically for thalidomide from Thalidomide Celgene, there was a significant deviation from dose proportionality when single oral doses were increased from 50 mg to 200 mg, with the increase in Cmax being approximately 30% less than expected in a linear system (Teo et al. 2001a).

For a conservative approach it was assumed that the deviation from proportionality in Cmax for Thalidomide Lipomed is only half that of Thalidomide Celgene (i.e. 15%) when increasing the dose from 100 mg to 200 mg.

Therefore Cmax,ss for Thalidomide Lipomed was estimated based on population-pharmacokinetic modelling, assuming 15% deviation from proportionality as justified above.

Based on the pop PK model when increasing the dose from 100 mg to 200 mg Cmax for the test product Thalidomide Lipomed was estimated to 2159 ng/mL(after a single dose) and to 2161 ng/mL.

(at steady state). This is consistent with the published data available indicating that mean Cmax,ss is almost identical with mean Cmax on day 1 and no accumulation or time dependency of the thalidomide pharmacokinetics has been noticed (Teo et al. 2004).

Published data regarding the lack of accumulation after repeated doses have been submitted indicating that single dose Cmax data are predictive for steady-state conditions (i.e. Cmax,ss).

A supportive analysis has been also conducted to support the lack of accumulation after the administration of the test product Thalidomide Lipomed based on observed PK data from the BE study after a single dose of 100 mg (including subject 016). The ratio of the partial area over the dosing interval ($AUC_{0-24,SD}$) to the AUC extrapolated to infinity ($AUC_{0-\infty,SD}$) observed for both test and reference products is 94 to 95% indicating that a low extent of accumulation can be expected for the test product.

In addition, it is confirmed that single dose Cmax data are predictive for steady-state conditions (i.e. Cmax,ss) also for test product.

In order to conduct the requested exposure safety analysis at the recommended therapeutic dose of 200 mg a comparison of the estimated values for Cmax of the test product Thalidomide Lipomed with published available literature data has been conducted indicating that estimated Cmax associated with the use of Thalidomide Lipomed at the recommended therapeutic dose of 200 mg is within the range of Cmax and Cmax,ss values assessed in publicly available studies investigating single and multiple oral doses of thalidomide 200 mg confirmed to be efficacious and safe.

A summary of high thalidomide dosages in other indications associated with high peak plasma concentrations has been presented, indicating that there were no safety issues which would suggest the presence of Cmax threshold toxicities. The published data include peak concentrations up to 11070 ng/ml which is several times higher than expected for Thalidomide Lipomed at the recommended therapeutic dose (200 mg) Therefore, there is no apparent increased risk of adverse drug reactions upon use of 200 mg Thalidomide Lipomed at steady state (Cmax,ss -2161 ng/mL) comparative with Thalidomide Celgene (1500 ng/ml).

Based on the pop PK model, the estimated Cmax,ss for the reference medicinal product after administration of multiple doses of 200 mg dose is around 1500 ng/ml, which is within the range reported in the published data regarding the Cmax,ss of the reference product Thalidomide Celgene also in healthy subjects, for which a mean Cmax,ss (2300 ± 330 ng/mL) is mentioned in the study conducted by Scheffler et. al 1999 and a mean Cmax,ss value of 1.2 mg/L (1200 ng/mL) reported in the study published by Teo et al. 2004.

After a single oral dose of thalidomide 100 mg administered orall,y it has been noted that C24 values after single oral dosing are similar with Ctau (=Cmin,ss) values predicted from modelling both for test and reference products. It is noted that in the absence of any relevant accumulation, as justified for the PK of thalidomide above, the C24 value after a single oral dose is very similar to Ctau (=Cmin,ss), C24 covering more than 90% of the Cmin,ss.

After single or multiple oral doses of thalidomide 200 mg, C24 and Ctau (=Cmin,ss) values for test product Thalidomide Lipomed were estimated based on pop PK model, thereby yielding C24 and Ctau (=Cmin,ss) values of 171 and 178 ng/mL, respectively. The estimates values for C24 and Ctau (=Cmin,ss) for the reference product Thalidomide Celgene 200 mg are also included.

The simulated values have been compared with the values form the publicly available studies investigating single and multiple oral doses of thalidomide 100 mg and 200 mg. The C24 and Ctau (=Cmin,ss) values associated with the use of Thalidomide Lipomed are within the range of C24 and

Ctau (=Cmin,ss) estimates reported in the public domain confirm to be efficacious and safe. This applies to a dose of 100 mg as well as to the recommended therapeutic dose of 200 mg.

In addition the estimated values for C24 and Ctau (=Cmin,ss) values associated with the use of the test product Thalidomide Lipomed at 200 mg are well above the values obtained after 100 mg dose for the reference medicinal product, therefore the efficacy is not compromised (171 and 178 ng/mL, respectively comparative with 70.38 and 70.10 ng/mL, respectively, considering that a dose of 100 mg per day is confirmed to be efficacious and safe for Thalidomide Celgene).

During the treatment with thalidomide no therapeutic drug monitoring is required to achieve a certain Cmin plasma concentration to assure efficacy.

Supporting publication has been also submitted concluding that there was no relationship between the concentration of thalidomide in the plasma and the efficacy (P >0.8).

Additional data has been also provided supporting that AUC parameter is more related with the efficacy and low trough (Cmin,ss) levels should be maintained to limit drug-related toxicities.

Considering Cmin,ss values for the test product Thalidomide Lipomed are lower that the values obtained for the reference product it could be concluded that fewer drug-related toxicities could be expected after administration of the test product, while the efficacy is similar based on AUC equivalence demonstrated in the conducted BE study.

The results of the comparative *in vitro* dissolution testing of the batches used in the conducted relative bioavailability study have been provided for three different buffers over the complete physiological pH range (pH 1.2, 4.5 and 6.8) with and without surfactant. As requested, the individual data on 12 units and variability have been submitted. Although the *in vitro* similarity has not been demonstrated, the *in vivo* results prevails and *in vitro* data is only complementary to the bioequivalence study.

One issue was identified regarding the reduction of the dose in case of peripheral neuropathy. As the medicinal product will be available only in one strength, i.e. 100 mg, and it is formulated as coated tablet, in case of neuropathy the reduced dose cannot be achieved. This issue was solved as at Day 121; the SmPC was revised specifying that "*for dose reductions below 100 mg, thalidomide-containing medicinal products with other strengths should be used*".

Overall, the AEs reported in the BE study are in line with the known safety profile of thalidomide. There were no apparent differences in safety profiles, except fatigue, which was reported slightly more in subjects after Test product administration than after Reference product administration.

2.4.2. Conclusions on clinical aspects

The BE study is pivotal for this application.

With respect to the primary endpoint Cmax, bioequivalence was not demonstrated. However, the differences in Cmax between the Test (one Thalidomide Lipomed 100 mg coated tablet) and Reference (two Thalidomide Celgene 50 mg hard capsules) formulations of thalidomide at the recommended therapeutic dose of 200 mg after a single dose and at steady state are not considered a safety problem.

Potential uncertainties related to Cmin and Ctau for efficacy have been adequately addressed and efficacy is not compromised for the test product despite the lower values achieved for Cmin and Ctau after the test product comparative with values achieved after the administration of the reference medicinal product after the administration of 100 mg and 200 mg doses, respectively.

Although the *in vitro* similarity has not been demonstrated, the *in vivo* results prevail.

2.5. Risk Management Plan

2.5.1. Safety concerns

Table 9: Summary of safety concerns

Important identified risks	• Teratogenicity • Severe infections (sepsis, septic shock and viral reactivation of hepatitis B) • Acute myeloid leukaemia (AML) and myelodysplastic syndromes (MDS)
Important potential risks	• Ischaemic heart disease (including myocardial infarction) • Other second primary malignancies (SPM) • Hepatic disorders (hepatocellular and cholestatic liver injury) • Off-label use • Medication error
Missing information	• None

2.5.2. Pharmacovigilance plan

Table 10. Summary table of additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 – Required additional pharmacovigilance activities				
Additional monitoring of implementation of the Thalidomide Lipomed Pregnancy Prevention Programme (PPP) Planned	Monitoring of Thalidomide Lipomed PPP implementation on a country-specific basis	Teratogenicity	Protocol submission	TBD – after agreement with respective NCA on methods and design
			Reporting of results	Periodically as of launch, in accordance with PSUR schedule
Monitoring of drug utilisation (demographics and indication) Planned	Collection of data to understand the demographics of the target population and indications for use of Thalidomide Lipomed Monitoring of off-label use	Teratogenicity Off-label use	Protocol submission	TBD – after agreement with respective NCA on methods and design
			Reporting of results	Periodically as of launch, in accordance with PSUR schedule
Patient materials comprehension validation Planned	Validation of comprehension of patient materials in countries where the reference medicinal product is not marketed (if applicable)	Teratogenicity	Reporting of results	Prior to launch in concerned countries (if applicable)

2.5.3. Risk minimisation measures

Table 11. Summary table of risk minimisation activities by safety concern

Safety concern	Risk minimisation measures
Teratogenicity	Routine risk minimisation measures: • Routine risk communication in SmPC Sections 4.3, 4.4, 4.6 and 4.8, in PL Section 2 and in boxed warning at the beginning of the PL, on outer packaging • Restricted medical prescription only • Limited supply (maximum 4 weeks for women of childbearing potential and 12 weeks for men and women of non-childbearing potential) Additional risk minimisation measures: Thalidomide Lipomed Pregnancy Prevention Programme: • Controlled distribution system • Educational materials (Educational healthcare professional booklet with patient assessment algorithm and pregnancy testing and contraception requirements; Treatment initiation forms and/or equivalent tool for women of childbearing potential, women of non-childbearing potential, and male patients; Educational brochures for patients (female and male); Patient cards and/or equivalent tools; Summary of product characteristics, package leaflet and labelling; Pregnancy reporting materials and information).
Severe infections (sepsis, septic shock, and viral reactivation of hepatitis B)	Routine risk minimisation measures: • Routine risk communication in SmPC Sections 4.4 and 4.8, in PL Sections 2 and 4 • Recommendation for specific clinical measures in SmPC Section 4.4 • Restricted medical prescription only Additional risk minimisation measures: • None
Acute myeloid leukaemia (AML) and myelodysplastic syndromes (MDS)	Routine risk minimisation measures: • Routine risk communication in SmPC Sections 4.4 and 4.8, in PL Sections 2 and 4 • Restricted medical prescription only Additional risk minimisation measures: • None

Safety concern	Risk minimisation measures
Ischaemic heart disease (including myocardial infarction)	Routine risk minimisation measures: • Routine risk communication in SmPC Sections 4.4 and 4.8, in PL Sections 2 and 4 • Recommendation for specific clinical measures in SmPC Section 4.2, in PL Sections 2 and 4 • Restricted medical prescription only Additional risk minimisation measures: • Educational materials (Educational healthcare professional booklet with patient assessment algorithm; Treatment initiation forms and/or equivalent tool; Educational brochures for patients; Patient cards and/or equivalent tools; Summary of product characteristics, package leaflet and labelling).
Other second primary malignancies (SPM)	Routine risk minimisation measures: • Routine risk communication in SmPC Section 4.4, in PL Section 2 • Restricted medical prescription only Additional risk minimisation measures: • None
Hepatic disorders (hepatocellular and cholestatic liver injury)	Routine risk minimisation measures: • Routine risk communication in SmPC Section 4.8, in PL Section 4 • Recommendation for specific clinical measures in SmPC Sections 4.2 and 4.4, PL Section 2 • Restricted medical prescription only Additional risk minimisation measures: • None
Off-label use	Routine risk minimisation measures: • Routine risk communication in SmPC Sections 4.1 and 4.4, in PL Section 1, on outer packaging, description of risks associated with the use of thalidomide throughout SmPC and in PL • Restricted medical prescription only Additional risk minimisation measures: • Controlled distribution system • Educational materials (Educational healthcare professional booklets with patient assessment algorithm, Educational brochures for patients, Treatment initiation forms, Summary of product characteristics, package leaflet and labelling; Patient cards and/or equivalent tools)

Safety concern	Risk minimisation measures
Medication error	Routine risk minimisation measures: • Routine risk communication in SmPC Section 4.2 Additional risk minimisation measures: • Educational materials (Educational healthcare professional booklets with patient assessment algorithm; Summary of product characteristics and labelling)

2.5.4. Conclusion

The CHMP considers that the risk management plan version 0.3 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

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Thalidomide Celgene (currently known as Thalidomide BMS). The bridging report submitted by the applicant has been found acceptable.

3. Benefit-Risk Balance

This application concerns a hybrid version of thalidomide hard capsules. The reference product Thalidomide Celgene (currently known as Thalidomide BMS) is indicated for the following therapeutic indication:

Thalidomide Celgene in combination with melphalan and prednisone is indicated as first line treatment of patients with untreated multiple myeloma, aged ≥ 65 years or ineligible for high dose chemotherapy.

Thalidomide Celgene is prescribed and dispensed in accordance with the Thalidomide Celgene Pregnancy Prevention Programme (see section 4.4 of the SmPC).

Non-clinical studies have not been provided for this application and this is considered adequate. 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 forms the pivotal basis with a single centre, open-label, randomised, balanced, 2-period, 2-sequence-crossover, single dose trial in healthy adult volunteers under fasting conditions. The study design is considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Thalidomide Lipomed 100 mg coated tablet does not meet the protocol-defined criteria for bioequivalence when compared with the Thalidomide Celgene 50 mg hard capsules. The point estimate and its 90% confidence interval for the parameter AUC0-tlast were all contained within the protocol-defined acceptance range of 80.00 to 125.00%. The point estimate for the parameter Cmax was contained within the protocol-defined acceptance range of 80.00 to 125.00%; however, its 90% confidence interval for the parameter Cmax was not contained within the protocol-defined acceptance range of 80.00 to 125.00% and its point estimate is 124.09%. Bioequivalence of the two formulations was not demonstrated.

However, the differences in Cmax between the Test (one Thalidomide Lipomed 100 mg coated tablet) and Reference (two Thalidomide Celgene 50 mg hard capsules) formulations of thalidomide at the recommended therapeutic dose of 200 mg after a single dose and at steady state are not considered a safety problem.

Potential uncertainties related to Cmin and Ctau for efficacy have been adequately addressed and efficacy is not compromised for the test product despite the lower values achieved for Cmin, and Ctau after the test product comparative with values achieved after the administration of the reference medicinal product after the administration of 100 mg and 200 mg doses, respectively. A benefit/risk ratio comparable to the reference product can therefore be concluded.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Thalidomide Lipomed is not similar to Kyprolis (carfilzomib), Imnovid (pomalidomide), Ninlaro (ixazomib), Farydak (panobinostat), Darzalex (daratumumab), Blenrep (belantamab mafodotin), Abecma (idecabtagene vicleucel) and Carvykti (ciltacabtagene autoleucel) within the meaning of Article 3 of Commission Regulation (EC) No.

847/2000.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Thalidomide Lipomed is favourable in the following indication(s):

Thalidomide Lipomed in combination with melphalan and prednisone is indicated as first line treatment of patients with untreated multiple myeloma, aged ≥ 65 years or ineligible for high dose chemotherapy.

Thalidomide Lipomed is prescribed and dispensed in accordance with the Thalidomide Lipomed Pregnancy Prevention Programme (see section 4.4 of the SmPC).

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 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**

Thalidomide Lipomed Pregnancy Prevention Programme (PPP) with controlled distribution system

The marketing authorisation holder (MAH) will implement a Pregnancy Prevention Programme (PPP) in each Member State where Thalidomide Lipomed is marketed. Details of the PPP will be agreed with the national competent authority (NCA) in each Member State and put in place prior to the launch of the medicinal product. The PPP will include implementation of a controlled distribution system in each concerned country, in agreement with the respective NCA, to ensure that all physicians and pharmacists who intend to prescribe or dispense Thalidomide Lipomed have access to the educational materials and are aware of the teratogenic properties and other important risks of thalidomide as well as the corresponding risk minimisation measures.

Educational Materials

The MAH will agree the contents of the Educational Healthcare Professional's Kit with the NCA in each Member State prior to launch of the medicinal product. In agreement with the respective NCAs, the Educational Healthcare Professional's Kit is proposed to contain the following educational materials and report forms:

1. Educational healthcare professional booklet with patient assessment algorithm and pregnancy testing and contraception requirements
2. Treatment initiation forms and/or equivalent tool for women of childbearing potential, women of non-childbearing potential, and male patients
3. Educational brochures for patients (female and male)
4. Patient cards and/or equivalent tools
5. Summary of product characteristics, package leaflet and labelling
6. Pregnancy reporting materials and information
7. Adverse reaction reporting forms.

The proposed key elements of each of these materials are described below.

Prior to approval by the NCA and launch of the medicinal product in countries where the reference product is not approved or marketed, the MAH will ensure that the educational materials for patients are provided to and reviewed by the national patients' organisations or if such an organisation does not exist or cannot be involved, by a relevant patients' group. Patients involved will be preferably naïve to the history of thalidomide. Results of the user testing will be provided to the NCA and final materials validated at a national level.

The MAH will notify the EMA and the appropriate national patients and victims' representatives of the proposed launch date before launch in each Member State.

Proposed key elements of the Educational Healthcare Professional's Kit

1. Educational healthcare professional booklet
    - History of thalidomide, background on Thalidomide Lipomed and its licensed indication
    - Posology
    - Maximum duration of treatment prescribed according to the approved indication dosing regimens
        - 4 weeks of treatment for women with childbearing potential
        - 12 weeks of treatment for men and for women without childbearing potential
    - Teratogenicity and the need to avoid foetal exposure
    - Guidance on handling the blisters or coated tablets of Thalidomide Lipomed for healthcare professionals and caregivers
    - Obligations of healthcare professionals who intend to prescribe or dispense Thalidomide Lipomed including
        - The need to provide comprehensive advice and counselling to patients
        - That patients should be capable of complying with the requirements for the safe use of thalidomide
        - Need to provide patients with the appropriate patient educational material
        - Report any pregnancy or adverse events to the MAH and the local health authority (if applicable to a Member State) using the provided forms
    - Safety advice relevant to all patients
        - Guidance to prevent medication errors (potential confusion with the reference medicinal product)
        - Description and management of ischaemic heart disease (including myocardial infarction)
        - Disposal of unwanted medicinal product
        - Not to donate blood during treatment (including during dose interruptions) and for at least 7 days following discontinuation of thalidomide

- Algorithm for Pregnancy Prevention Programme implementation
  - This shall assist with patient categorisation and determination of required pregnancy prevention and testing measures
- Pregnancy Prevention Programme information
  - Definition of women of childbearing potential and actions the prescriber should take if unsure
  - Information on what is effective contraception
  - Safety advice for women of childbearing potential
    - Need to avoid foetal exposure
    - Pregnancy prevention requirement, definition and need for adequate contraceptive methods
    - 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 thalidomide
      - The physician prescribing thalidomide that she has stopped or changed her method of contraception
    - Pregnancy testing requirements
      - Advice on suitable tests
      - Frequency (before commencing, monthly during treatment and after finishing treatment)
    - Need to stop thalidomide 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
    - That thalidomide is found in semen and the need to use condoms if sexual partner is pregnant or is a woman of childbearing potential not using effective contraception
    - That if his partner becomes pregnant he should inform his treating doctor immediately and always use a condom during intercourse
    - That he should not donate semen during treatment (including during dose interruptions) and for at least 7 days following discontinuation of thalidomide
- Pregnancy reporting requirements
  - Instruction to stop thalidomide immediately upon suspicion of pregnancy, if female patient
  - Need to refer patient to physician specialised or experienced in dealing with teratology for advice and evaluation
  - Complete pregnancy reporting form as provided in the "Educational Healthcare Professional's Kit"
  - Local contact details for reporting of any suspected pregnancy

2. <u>Treatment initiation forms and/or equivalent tool</u>
   - There will be 3 types of treatment initiation forms and/or equivalent tool:
     - Women of childbearing potential
     - Women of non-childbearing potential
     - Male patients
   - All treatment initiation forms and/or equivalent tool will contain the following elements:
     - Teratogenicity warning
     - Patients receive appropriate counselling prior to treatment initiation
     - Date of counselling
     - Affirmation of patient understanding regarding the risk of thalidomide and the PPP measures
     - 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 treatment initiation 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 thalidomide. 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."

- Treatment initiation forms and/or equivalent tool for women of childbearing potential will 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 thalidomide
    - The need for effective contraception, 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 on thalidomide
      - The physician prescribing thalidomide that she has stopped or changed her method of contraception
    - The need for pregnancy tests, i.e. before treatment, at least every 4 weeks during treatment and after treatment
    - The need to stop thalidomide immediately upon suspicion of pregnancy
    - The need to contact her doctor immediately upon suspicion of pregnancy
    - That she should not share the treatment 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 thalidomide
    - That she should return any unused product to the pharmacist at the end of treatment
- Treatment initiation forms and/or equivalent tool for women with no childbearing potential will also include:
  - Confirmation that the physician has discussed the following:
    - That she should not share the treatment 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 thalidomide
    - That she should return any unused product to the pharmacist at the end of treatment
- Treatment initiation forms and/or equivalent tool for male patients will also include:
  - Confirmation that the physician has discussed the following:
    - The need to avoid foetal exposure
    - That thalidomide is found in semen and the need to use condoms if sexual partner is pregnant or is a woman with childbearing potential not on effective contraception
    - That if his partner becomes pregnant he should inform his treating doctor immediately and always use a condom
    - That he should not donate blood or semen during treatment (including during dose interruptions) and for at least 7 days following discontinuation of thalidomide
    - That he should not share the treatment with any other person
    - That he should return any unused product to the pharmacist at the end of treatment

3. <u>Educational brochures for patients:</u>
   - There will be 3 types of educational brochures for patients:
     - Brochure for women of childbearing potential
     - Brochure for women who are not of childbearing potential
     - Brochure for male patients
   - All educational brochures for patients will contain the following information:
     - That thalidomide is teratogenic
     - That thalidomide may cause ischaemic heart disease (including myocardial infarction)

    - Description of the patient card and its use in the individual Member State
    - Guidance on handling Thalidomide Lipomed for patients, caregivers and family members
    - National or other applicable specific arrangements for a prescription for thalidomide to be dispensed
    - That thalidomide must not be given to any other person
    - That the patient should not donate blood
    - That the patients should tell their doctor about any adverse events
    - That any unused product should be returned to the pharmacist at the end of the treatment
- In addition to the above information contained in all educational brochures, the educational brochures for women of childbearing potential will also include the following information:
    - The need to avoid foetal exposure
    - The need for 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 thalidomide
        - The physician prescribing thalidomide that she has stopped or changed her method of contraception
    - The need for pregnancy tests, i.e. before treatment, at least every 4 weeks during treatment and at least 4 weeks after treatment
    - The need to stop thalidomide immediately upon suspicion of pregnancy
    - The need to contact her doctor immediately upon suspicion of pregnancy
- In addition to the above information contained in all educational brochures, the educational brochures for male patients will also include the following information:
    - The need to avoid foetal exposure
    - That thalidomide is found in semen and the need to use condoms if sexual partner is pregnant or is a woman with childbearing potential not on effective contraception
    - That if his partner becomes pregnant he should inform his treating doctor immediately and always use a condom
    - That he should not donate semen during treatment (including during dose interruptions) and for at least 7 days following discontinuation of thalidomide

4. Patient cards and/or equivalent tools:
    - 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)
    - Verification of initial negative pregnancy test prior to start of treatment (if woman of childbearing potential)
    - Pregnancy test dates and results

5. Summary of product characteristics, package leaflet and labelling

6. Pregnancy initial and outcome reporting forms

7. Adverse reaction reporting forms

8. Post-marketing and compliance assessment (as applicable to a Member State)

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

The Member States must ensure that all conditions or restrictions with regard to the safe and effective use of the medicinal product described below are implemented:

1. The Member States shall agree the details of a controlled distribution system with the MAH according to national regulations and healthcare systems and must implement such programme nationally before launch of the medicinal product to ensure that:
    - Prior to prescribing all healthcare professionals who intend to prescribe (and in agreement with the National Competent Authority, dispense) Thalidomide Lipomed are provided with an Educational Healthcare Professional's Kit containing the following:
        - Educational healthcare professional booklet with patient assessment algorithm and pregnancy testing and contraception requirements
        - Treatment initiation forms and/or equivalent tool for women of childbearing potential, women of non-childbearing potential, and male patients
        - Educational brochures for patients (female and male)
        - Patient cards and/or equivalent tools
        - Summary of product characteristics, package leaflet and labelling
        - Pregnancy reporting materials and information
        - Adverse reaction reporting forms.

2. The Member States shall put into place measures to ensure that:
    - The maximum treatment duration for one prescription shall be
        - 4 weeks for women with childbearing potential
        - 12 weeks for men and women without childbearing potential
    - Prescriptions can only be dispensed within 7 days of the date of the prescription

3. The Member States shall ensure that the MAH implements a pregnancy prevention programme (PPP) within their territory. Details of how the PPP will be implemented should be agreed with the Marketing Authorisation Holder and put in place prior to the marketing of the product.

4. The Member States should agree the local implementation of the patient card system

5. The Member States should ensure that the MAH provides the educational materials to the national patients' organisations for review or if such an organisation does not exist or can not be involved, to a relevant patients group. Patients involved should be preferably naïve to the history of thalidomide. Results of the user testing will have to be provided to the national competent authority and final materials validated at a national level.

6. The Member State should agree with the Marketing Authorisation Holder prior to the launch of the product:

- The most appropriate strategies to monitor the off label use within national territory
- The collection of detailed data to understand demographics of target population, indication and number of women of childbearing potential in order to monitor closely the off-label use within national territory
- The set-up of national measures to assess the effectiveness of and compliance with the PPP.

7. The Member States shall ensure that the following key elements are included in the appropriate material (key elements of the Educational Healthcare professional's kit):

<u>a-Educational healthcare professional booklet</u>

- History of thalidomide, background on Thalidomide Lipomed and its licensed indication
- Posology
- Maximum duration of treatment prescribed according to the approved indication dosing regimens
  - 4 weeks of treatment for women with childbearing potential
  - 12 weeks of treatment for men and for women without childbearing potential
- Teratogenicity and the need to avoid foetal exposure
- Guidance on handling the blisters or coated tablets of Thalidomide Lipomed for healthcare professionals and caregivers
- Obligations of healthcare professionals who intend to prescribe or dispense Thalidomide Lipomed including
  - The need to provide comprehensive advice and counselling to patients
  - That patients should be capable of complying with the requirements for the safe use of thalidomide
  - Need to provide patients with the appropriate patient educational material
  - Report any pregnancy or adverse events to the MAH and the local health authority (if applicable to a Member State) using the provided forms
- Safety advice relevant to all patients
  - Guidance to prevent medication errors (potential confusion with the reference medicinal product)
  - Description and management of ischaemic heart disease (including myocardial infarction)
  - Disposal of unwanted medicinal product
  - Not to donate blood during treatment (including during dose interruptions) and for at least 7 days following discontinuation of thalidomide
- Algorithm for Pregnancy Prevention Programme implementation
  - This shall assist with patient categorisation and determination of required pregnancy prevention and testing measures

- Pregnancy Prevention Programme information
    - Definition of women of childbearing potential and actions the prescriber should take if unsure
    - Information on what is effective contraception
    - Safety advice for women of childbearing potential
        - Need to avoid foetal exposure
        - Pregnancy prevention requirement, definition and need for adequate contraceptive methods
        - 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 thalidomide
            - The physician prescribing thalidomide that she has stopped or changed her method of contraception
        - Pregnancy testing requirements
            - Advice on suitable tests
            - Frequency (before commencing, monthly during treatment and after finishing treatment)
        - Need to stop thalidomide 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
        - That thalidomide is found in semen and the need to use condoms if sexual partner is pregnant or is a woman of childbearing potential not using effective contraception
        - That if his partner becomes pregnant he should inform his treating doctor immediately and always use a condom during intercourse
        - That he should not donate semen during treatment (including during dose interruptions) and for at least 7 days following discontinuation of thalidomide
- Pregnancy reporting requirements
    - Instruction to stop thalidomide immediately upon suspicion of pregnancy, if female patient
    - Need to refer patient to physician specialised or experienced in dealing with teratology for advice and evaluation
    - Complete pregnancy reporting form as provided in the "Educational Healthcare Professional's Kit"
    - Local contact details for reporting of any suspected pregnancy

b- <u>Treatment initiation forms and/or equivalent tool</u>

- There will be 3 types of treatment initiation forms and/or equivalent tool:

- Women of childbearing potential
- Women of non-childbearing potential
- Male patients

- All treatment initiation forms and/or equivalent tool will contain the following elements:
  - Teratogenicity warning
  - Patients receive appropriate counselling prior to treatment initiation
  - Date of counselling
  - Affirmation of patient understanding regarding the risk of thalidomide and the PPP measures
  - 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 treatment initiation 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 thalidomide. 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."
- Treatment initiation forms and/or equivalent tool for women of childbearing potential will 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 thalidomide
    - The need for effective contraception, 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 on thalidomide
      - The physician prescribing thalidomide that she has stopped or changed her method of contraception
    - The need for pregnancy tests, i.e. before treatment, at least every 4 weeks during treatment and after treatment
    - The need to stop thalidomide immediately upon suspicion of pregnancy
    - The need to contact her doctor immediately upon suspicion of pregnancy
    - That she should not share the treatment 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 thalidomide
    - That she should return any unused product to the pharmacist at the end of treatment

- Treatment initiation forms and/or equivalent tool for women with no childbearing potential will also include:
    - Confirmation that the physician has discussed the following:
        - That she should not share the treatment 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 thalidomide
        - That she should return any unused product to the pharmacist at the end of treatment
- Treatment initiation forms and/or equivalent tool for male patients will also include:
    - Confirmation that the physician has discussed the following:
        - The need to avoid foetal exposure
        - That thalidomide is found in semen and the need to use condoms if sexual partner is pregnant or is a woman with childbearing potential not on effective contraception
        - That if his partner becomes pregnant he should inform his treating doctor immediately and always use a condom
        - That he should not donate blood or semen during treatment (including during dose interruptions) and for at least 7 days following discontinuation of thalidomide
        - That he should not share the treatment with any other person
        - That he should return any unused product to the pharmacist at the end of treatment

c- <u>Educational brochures for patients:</u>

- There will be 3 types of educational brochures for patients:
    - Brochure for women of childbearing potential
    - Brochure for women who are not of childbearing potential
    - Brochure for male patients
- All educational brochures for patients will contain the following information:
    - That thalidomide is teratogenic
    - That thalidomide may cause ischaemic heart disease (including myocardial infarction)
    - Description of the patient card and its use in the individual Member State
    - Guidance on handling Thalidomide Lipomed for patients, caregivers and family members
    - National or other applicable specific arrangements for a prescription for thalidomide to be dispensed
    - That thalidomide must not be given to any other person
    - That the patient should not donate blood
    - That the patients should tell their doctor about any adverse events
    - That any unused product should be returned to the pharmacist at the end of the treatment

- In addition to the above information contained in all educational brochures, the educational brochures for women of childbearing potential will also include the following information:
    - The need to avoid foetal exposure
    - The need for 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 thalidomide
        - The physician prescribing thalidomide that she has stopped or changed her method of contraception
    - The need for pregnancy tests, i.e. before treatment, at least every 4 weeks during treatment and at least 4 weeks after treatment
    - The need to stop thalidomide immediately upon suspicion of pregnancy
    - The need to contact her doctor immediately upon suspicion of pregnancy
- In addition to the above information contained in all educational brochures, the educational brochures for male patients will also include the following information:
    - The need to avoid foetal exposure
    - That thalidomide is found in semen and the need to use condoms if sexual partner is pregnant or is a woman with childbearing potential not on effective contraception
    - That if his partner becomes pregnant he should inform his treating doctor immediately and always use a condom
    - That he should not donate semen during treatment (including during dose interruptions) and for at least 7 days following discontinuation of thalidomide

d- Patient cards and/or equivalent tools:

- 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)
- Verification of initial negative pregnancy test prior to start of treatment (if woman of childbearing potential)
- Pregnancy test dates and results

e- Summary of product characteristics, package leaflet and labelling

f- Pregnancy initial and outcome reporting forms

g- Adverse reaction reporting forms

h- Post-marketing and compliance assessment (as applicable to a Member State)

These conditions fully reflect the advice received from the PRAC.