17 December 2015
EMA/CHMP/6613/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Neofordex

International non-proprietary name: dexamethasone

Procedure No. EMEA/H/C/004071/0000

Note

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

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List of abbreviations

AE Adverse Event

ASCT Autologous Stem Cell Transplantation

AUC Area Under the Curve

Bor Bortezomib

BMI Body Mass Index

BMSC Bone marrow stromal cells

BTD PACE Bortezomib, Thalidomide, and Dexamethasone plus Cisplatin, Doxorubicin, Cyclophosphamide, and Etoposide

CEP Certificate of Suitability of the EP

CHMP Committee for Human Medicinal Products

CI Confidence Interval

CL Total Clearance

Cmax Average Maximum Concentration

CR Complete Response

CTD Cyclophosphamide, Thalidomide, and Dexamethasone

CTDa Attenuated Cyclophosphamide, Thalidomide, and Dexamethasone

CVAD Cyclophosphamide, Vincristine, Adriamycin and Dexamethasone

CYP Cytochrome

DCEP Dexamethasone, Cyclophosphamide, Etoposide, and Cisplatin,

Dex Dexamethasone

DOR Duration of Response

EBMT European Group for Blood and Marrow Transplantation

EC European Commission

ECOG Eastern Cooperative Oncology Group

EDQM European Directorate for the Quality of Medicines

EFS Event Free Survival

GCP Good Clinical Practice

GD Gestation days

HPLC High performance liquid chromatography

HR Hazard Ratio

ICH	International Conference on Harmonisation
IκBα	Inhibitor of κB α
IL-6	Interleukin-6
IMiD	Immunomodulatory Drug
IMWG	International Myeloma Working Group
INN	International Nonproprietary Name
IV	Intravenous
Len	Lenalidomide
LenDex	Lenalidomide plus Dexamethasone
MAA	Marketing Authorisation Application
MM	Multiple Myeloma
MP	Melphalan plus Prednisone
MR	Minimal Response
MPR	Melphalan, Prednisone, and Lenalidomide
MPT	Melphalan, Prednisone, and Thalidomide
MTD	Maximum Tolerated Dose
N	Total Number of Patients
NA	Not Applicable
nCR	Near Complete Response
NF κB	Nuclear Factor Kappa-light-chain-enhancer of activated B cells
NR3C1	Glucocorticoid Receptor Gene
OPA	Oriented polyamide film
ORR	Overall Response Rates
OS	Overall Survival
PACE	Cisplatin, Doxorubicin, Cyclophosphamide, and Etoposide Methasone.
PFS	Progression Free Survival
Ph. Eur.	European Pharmacopoeia
PN	Peripheral Neuropathy
PND	Postnatal day
PR	Partial Response
Pred	Prednisone
PRS	Post Relapse Survival

PVC	Poly vinyl chloride
PVDC	Polyvinylidene chloride
Rd	Rd, lenalidomide plus low-dose dexamethasone
RH	Relative humidity
RMP	Risk Management Plan
RR	Relapsed/Refractory
SCT	Stem Cell Transplant
SD	Stable Disease
SDS	Sodium Dodecyl Sulfate
SmPC	Summary of Product Characteristics
SOC	System Organ Class
TD	Thalidomide and Dexamethasone
Thal	Thalidomide
ThalDex	Thalidomide plus Dexamethasone
TK	Thymidine kinase
TLC	Thin layer chromatography
Tmax	Time of Maximum Concentration
TNT	Time to Next Therapy
TRAIL	TNF-related apoptosis-inducing ligand
TSE	Transmissible Spongiform Encephalopathy
TT3	Total Therapy 3
TTP	Time to Progression
TTR	Time to Response
VAD	Vincristine, Adriamycin/Doxorubicin and Dexamethasone
VGPR	Very Good Partial Response
VTD	Bortezomib, Thalidomide, and Dexamethasone
XRPD	X-Ray Powder Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Laboratoires CTRS submitted on 7 November 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Neofordex, through the centralised procedure under Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 September 2014.

The applicant applied for the following indication: Neofordex is indicated in adults for the treatment of symptomatic multiple myeloma in combination with other medicinal products.

Neofordex was designated as an orphan medicinal product EU/3/10/745 on 9 June 2010 in the following indication: Treatment of multiple myeloma.

Following the CHMP positive opinion and at the time of the review of the orphan designation by the Committee on Orphan Medicinal Products (COMP), this product was withdrawn from the Community Register of designated orphan medicinal products on 25.01.2016 on request of the sponsor.

The application concerns a hybrid medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product (Dectancyl) for which a Marketing Authorisation is or has been granted in a Member State on the basis of a complete dossier.

The legal basis for this application refers to:

Hybrid application (Article 10(3) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data, a bioequivalence study with the reference medicinal product Dectancyl and appropriate non-clinical data. The applicant also provided a letter of consent from Celgene Europe Limited who has granted permission to use their clinical data for the purpose of the marketing authorisation for Neofordex.

Information on paediatric requirements

Not applicable.

Information relating to orphan market exclusivity

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.

Scientific Advice/Protocol Assistance

The applicant did not seek Scientific Advice or Protocol Assistance at the CHMP.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Robert James Hemmings, Co-Rapporteur: Daniela Melchiorri

- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 February 2015. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 13 February 2015.
- During the meeting on 12 March 2015 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan.
- During the meeting on 26 March 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 26 March 2015.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 24 July 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 24 August 2015.
- During the CHMP meeting on 24 September 2015, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 19 October 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 28 October 2015.
- During the CHMP meeting on 19 November 2015, the CHMP agreed on a second list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the second CHMP List of Outstanding Issues on 25 November 2015.
- Following a written procedure, the Pharmacovigilance Risk Assessment Committee (PRAC) adopted on 10 December 2015 the PRAC Advice on the submitted Risk Management Plan.
- During the meeting on 17 December 2015, 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 Neofordex. The CHMP also adopted an assessment report on similarity of Neofordex with the following authorised orphan medicinal products: Revlimid, Thalidomide Celgene, Imnovid, Farydak and Kyprolis.

2. Scientific discussion

2.1. Introduction

Multiple myeloma is a neoplastic plasma-cell disorder that is characterised by clonal proliferation of malignant plasma cells in the bone marrow microenvironment, monoclonal protein in the blood or urine, and associated organ dysfunction. Symptomatic multiple myeloma is characterised by hypercalcaemia, renal impairment, anaemia and bony lesions (collectively known as ''CRAB''). Multiple myeloma is primarily a disease of the elderly, with a median age at diagnosis of around 70 years. 37% of patients are younger than 65 years, 26% are between the ages of 65 and 74 years, and 37% are 75 years of age or older. In patients presenting when less than 60 years of age, 10-year survival is approximately 30% (Palumbo and Anderson 2011).

High dose chemotherapy (e.g. melphalan) followed by autologous stem cell transplant (HDT-ASCT) is the standard of care for previously untreated symptomatic multiple myeloma in patients under the age of 65 years. Various induction regimens are utilised prior to HDT-ASCT, or in patients ineligible for HDT-ASCT. Various regimens are also used in the consolidation, maintenance and relapsed / refractory settings. Historically, regimens such as melphalan + prednisolone (Salmon 1967) or vincristine + doxorubicin + dexamethasone (VAD) have been used.

In recent years, the introduction of the immunomodulatory drugs (IMiDs) such as thalidomide, lenalidomide and pomalidomide, and the proteasome inhibitor bortezomib have changed the management of myeloma and extended overall survival. In Europe, Revlimid (lenalidomide) and Velcade (bortezomib) are approved in combination with high dose oral dexamethasone for the treatment of multiple myeloma.

In a more advanced setting of Relapsed/Refractory Multiple Myeloma (RRMM), for patients who have received at least 2 prior therapies, including bortezomib and an IMiD, and have shown relapsed or refractory disease, pomalidomide (+dex) and panobinostat (+bortezomib + dex) are approved agents in the EU.

The proteasome inhibitor carfilzomib in combination with lenalidomide and dexamethasone was approved in the EU for the treatment of adult patients with multiple myeloma who have Dexamethasone is a synthetic glucocorticoid; it combines high anti-inflammatory effects with low mineralocorticoid activity. At high doses (e.g. 40 mg), it reduces the immune response (SmPC section 5.1).

Dexamethasone has been shown to induce multiple myeloma cell death (apoptosis) via a down-regulation of Nuclear Factor-κB activity and an activation of caspase-9 through second mitochondria-derived activator of caspase (Smac; an apoptosis promoting factor) release. Prolonged exposure was required to achieve maximum levels of apoptotic markers along with increased caspase-3 activation and DNA fragmentation. Dexamethasone also down-regulated anti apoptotic genes and increased IκB-α protein levels (SmPC section 5.1).

Dexamethasone apoptotic activity is enhanced by the combination with thalidomide or its analogues and with proteasome inhibitor (e.g. bortezomib). Neofordex 40 mg tablets is a high dose oral dexamethasone formulation developed for use in adults for the treatment of symptomatic multiple myeloma in combination with other medicinal products. It is designed to be taken once daily as pulse therapy (for example days 1-4, 9-12 and 17-20 of a 28 day cycle). Dexamethasone tablet formulations currently approved in member states range from 0.5 mg to 8.0 mg strength (SmPC section 5.1).

The applicant applied for a marketing authorisation for the following indication which has been agreed by the CHMP: Neofordex is indicated in adults for the treatment of symptomatic multiple myeloma in combination with other medicinal products (SmPC section 4.1).

The dose and administration frequency varies with the therapeutic protocol and the associated treatment(s). Neofordex administration should follow instructions for dexamethasone administration when described in the Summary of Product Characteristics of the associated treatment(s). If this is not the case, local or international treatment protocols and guidelines should be followed. Prescribing physicians should carefully evaluate which dose of dexamethasone to use, taking into account the condition and disease status of the patient.

The usual posology of dexamethasone is 40 mg once per day of administration.

At the end of dexamethasone treatment, the dose should be tapered in a stepwise fashion until a complete stop.

In elderly and/or frail patients, the daily dose may be reduced to 20 mg of dexamethasone, according to the appropriate treatment regimen (SmPC section 4.2).

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as tablets containing dexamethasone acetate, equivalent to 40 mg dexamethasone as active substance. The tablets can be divided into two halves for administration of a 20 mg dose.

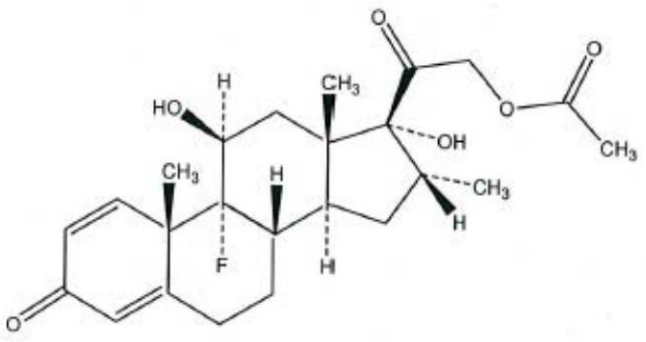
Other ingredients are: lactose monohydrate, microcrystalline cellulose, magnesium stearate, colloidal anhydrous silica.

The product is available in OPA/Aluminium /PVC-Aluminium perforated unit dose blisters as described in section 6.5 of the SmPC.

2.2.1. Active substance

General information

The chemical name of the active substance is dexamethasone acetate corresponding to the molecular formula $C_{24}H_{31}FO_6$. It has a relative molecular mass of 434.5 g/mol and has the following structure:



Dexamethasone acetate is a white or almost white crystalline powder, practically insoluble in water, and freely soluble in methanol, ethanol and acetone.

Dexamethasone acetate exhibits stereoisomerism due to the presence of eight chiral centres. Enantiomeric purity is controlled routinely by optical rotation.

There is a monograph for dexamethasone acetate in the European Pharmacopoeia. The manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for dexamethasone acetate which has been provided within the current Marketing Authorisation Application.

Manufacture, characterisation and process controls

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

Further data were provided on particle size and shape characterisation and on morphology. Dexamethasone acetate exhibits polymorphism; four different crystal forms have been described: two true polymorphs (form I and form II) and two hydrated forms (mono- and sesquihydrate). Possible phase transitions depending on temperature and humidity conditions were described. It was concluded that, starting from Form II, a sesquihydrate form (1.5 water equivalent per active substance molecule) is generated first under high relative humidity conditions, without forming the monohydrate. This sesquihydrate can then, according to the conditions, either revert to Form II, or give the monohydrate. Form I, the more stable form, can only be generated from Form II at high temperature, but not from the hydrated forms. Intrinsic Dissolution Rates (IDR) of the different polymorphs were studied.

The morphology of the active substance produced by the active ingredient manufacturer is determined and controlled by an XRPD method with a test and control limits included within the specification for the active substance.

Specification

The control tests comply with the specification and test methods of the Ph. Eur. Monograph for dexamethasone acetate and additional test mentioned in the CEP. Additional specifications have also been set for particle size (laser diffraction) and polymorphism (XRPD). All additional methods have been adequately validated and described according to ICH Q2.

Control limits for particle size distribution and morphology are justified in view of the characteristics of the batch of active substance used for the bioequivalence study.

Batch analysis data from two production scale batches of the active substance have been provided. The results are within the specifications and consistent from batch to batch.

Stability

The CEP for this source confirmed a retest period of up to 5 years, when stored in the proposed commercial pack.

2.2.2. Finished medicinal product

Description of the product and Pharmaceutical development

The dexamethasone 40 mg tablet was developed to enhance patient convenience in the treatment of multiple myeloma (MM) by providing a high strength oral formulation compared to other formulations available in the EU market. In addition these tablets are scored to enable posology adjustment and administration of a 20 mg dose, when required. Due to concerns over the stability of the unpackaged, sub-divided tablet, the unused half tablet should be discarded (see also stability of the product section below). Despite this instruction, there is a risk that in practice, the spare half tablet may be retained and administered subsequently. In addition, there is also a concern on the difficulty that elderly and frail patients may have to sub-divide the tablets. In order to address these, the applicant committed to submit a marketing authorisation application (MAA) for a 20 mg oral dosage form with an indication in MM in order to eliminate the need to break the 40 mg tablets if a 20 mg dose is prescribed. A variation application should be submitted within 12 months of the first approval of a marketing authorisation for the 20 mg oral dosage form to eliminate the score line of the 40 mg tablet (see Risk Management Plan).

The finished product composition includes dexamethasone acetate, lactose monohydrate, microcrystalline cellulose, colloidal anhydrous silica and magnesium stearate.

Tablet formulations of dexamethasone with different qualitative and quantitative compositions were manufactured and studied to determine the formulation and method of manufacture that contribute to a pharmaceutically acceptable and stable product.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. In addition particle size distribution is controlled for microcrystalline cellulose and lactose monohydrate. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

Given the extremely poor aqueous solubility of the active substance, in vivo absorption is likely to be limited by dissolution rate.

Bioequivalence of Neofordex 40 mg Tablet versus the reference product, Dectancyl 0.5 mg tablets was investigated utilising a 20 mg total dose for each arm. Neofordex 40 mg tablets were sub-divided to provide the 20 mg dose. The applicant has provided a justification for a biowaiver for the 40mg dose, on the basis that the conditions laid out in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98) are fulfilled. As the 20 mg dose, is simply a sub-division of the 40 mg dose, and the tablet disintegrates quickly (< 15 minutes), the biowaiver is considered acceptable.

The development of the dissolution test proposed for routine Quality Control (QC) was described and the discriminatory power of the method was studied. The study performed showed that the dissolution method is discriminatory for tablets of different hardness. Dexamethasone acetate is known to exhibit polymorphism therefore several studies were performed to investigate the discriminatory power of the dissolution method regarding polymorphism. No comprehensive summary of data was provided to correlate the physical properties of the tablets (polymorphic ratio, hardness, water content) and their dissolution properties. Data provided suggest that the dissolution method is not discriminatory to the morphology of the active substance. As a result and, in the absence of in-vitro/in-vivo correlation studies, tests and control limits for detection of one of the polymorphic form by XRPD and water content were included in the finished product specifications at batch release and at the end of shelf-life. This will ensure that polymorphic composition of the active substance does not change during the

manufacture of the finished product and is consistent with the polymorphic form present in the bioequivalence study batch. In the absence of demonstration of the discriminatory power of the method toward active substance particle size distribution, stringent control limits were applied to active substance particle size distribution, based on the particle size distribution of active substance used in the batch used for the bioequivalence study.

The primary packaging is a OPA/Aluminium /PVC-Aluminium perforated unit dose blister. The blister pack has perforations facilitating the separation of a packaged unit dose, suitable for the purposes of multi-dose compliance aids. The blister material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product since it provides an effective barrier to environmental humidity.

Manufacture of the product and process controls

The manufacturing process consists of three main steps: dry mixing of the constituents followed by direct compression and packaging. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated on four production scale batches. Manufacturing conditions chosen prevent polymorphic form change. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process pharmaceutical form.

Product specification

The finished product specifications include appropriate tests for this kind of dosage form: appearance, identification (TLC, HPLC), mean mass (Ph. Eur.), resistance to crushing (Ph. Eur.), residual humidity content (thermogravimetry), absence of other detectable polymorph (XRPD), disintegration (Ph. Eur.), dissolution (Ph. Eur.), assay (HPLC), content uniformity of dosage units (Ph. Eur.), divisibility test of tablets (Ph. Eur.), degradation products (HPLC) and microbial contamination (Ph. Eur.).

The analytical methods have been adequately described and appropriately validated in accordance with the ICH guidelines except for the XRPD method. The CHMP recommends that prior to commercialisation, the applicant generate satisfactory test method validation for XRPD method in line with the protocol submitted during procedure.

Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results were provided for several batches including two pilot scale batches and three production scale batches manufactured at the proposed manufacturing site, confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data were provided for two production scale batches of finished product stored for up to 18 months under long term conditions at 25 ºC / 60% RH, up to 12 months under intermediate conditions at 30 ºC / 65% RH, and for up to 6 months under accelerated conditions at 40 ºC / 75% RH, according to the ICH guidelines. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Supportive stability data were also provided for batches manufactured on another site than the one proposed for marketing or packed in different primary packaging that the one proposed for marketing.

For the primary stability batches, samples were tested for appearance, average unit mass, dissolution, disintegration of tablets, residual humidity content, resistance to crushing of tablets, assay, impurities and microbiological quality. The analytical procedures for determination of degradation products have been shown to be stability indicating. Tests for uniformity of content on subdivided tablets were not performed; however this has been adequately demonstrated in the supportive stability lots.

Out of specification dissolution results after 3 months storage at 40°C/75%RH were observed for the supportive stability batches stored in the PVC/PVdC blister presentation. However no significant changes have been observed for the finished product with the primary packaging proposed for marketing confirming the choice of the packaging material.

In view of this, additional stability data were requested during the procedure to demonstrate absence of any other polymorphic form other than the desired one. Data from two batches of finished product, stored in the primary packaging proposed for marketing at an 18 month time point at 30°C/65%RH and 40°C/75%RH were provided. The justification provided by the applicant for the absence of XRPD analysis in the stability study for the product stored at 25°C/65%RH was considered acceptable.

In light of these data, a shelf-life of up to 24 months with no special temperature storage condition, as stated in the SmPC, was considered to be acceptable.

No photostability data have been presented for the finished product. The active substance is known to be photosensitive, which is reflected by inclusion of "protect from light" statements in the Ph. Eur. monograph for dexamethasone acetate and the BP monograph for dexamethasone tablets. This is confirmed by the results of forced degradation studies. As a result, the applicant's proposal not to perform studies on the finished product, but to include a storage precaution in the SmPC was accepted.

Stability of sub-divided, unpackaged tablets

Stability data have been provided for a single lot of sub-divided tablets stored for 15 days at 25°C/60%RH, 30°C/65%RH and 30°C/75%RH in the following presentations: a "weighing plate", a HDPE container with desiccant, a PVC/PVdC blister. Only the open-dish study was considered to satisfactorily simulate the potential environment that a sub-divided tablet that has been removed from its packaging would encounter. All test parameters remained with the proposed control limits; however a decrease in extent of release was apparent for tablets stored at 30°C/75%RH. It was noted that XRPD analysis was not performed in this study to confirm an absence of polymorphic change. Nevertheless, during the studies performed to evaluate the discriminatory power of the dissolution method, substantial changes in dissolution performance were observed for unpackaged product exposed to accelerated conditions of 40°C/75%RH for a total of 12 days. XRPD analysis on those samples showed that the changes in dissolution performance were consistent with polymorphic transitions and they have potential to impact bioavailability. Following CHMP request, the Applicant developed an XPRD method to quantify one of the polymorphic forms in the finished product. Using this method, conversion of dexamethasone polymorphic form has been studied under a range of "open dish" conditions. Under open-dish conditions, particularly at 84% humidity, tablet integrity was significantly disrupted, such that tablet crushing strength was no longer measurable, and corresponding dissolution results were within the specification limits. It was noticed that these data conflict somewhat with the results of the dissolution discrimination studies that were provided at the submission of this application to evaluate the impact on dissolution performance of open-dish exposure

to a range of environmental conditions. Taking into account the latest stability data provided during the procedure and following CHMP request, the applicant withdrew the initial proposal for a two week in-use shelf-life for halved tablets and agreed to have the following storage precaution in the SmPC "Halved tablets that are not taken immediately should be disposed of".

Based on available stability data, the proposed shelf-life of 24 months with no special temperature storage condition and the following storage conditions are acceptable: "Tablets should be kept in the blister package until administration. Individual tablets in intact packaging should be separated from the blister using the perforation, e.g. for use in multi-compartment compliance aids. Halved tablets that are not taken immediately should be disposed of", as stated in the SmPC (section 6.4)".

Adventitious agents

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

2.2.3. Discussion on chemical, and pharmaceutical aspects

There is a monograph for dexamethasone acetate in the European Pharmacopoeia. The manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for dexamethasone acetate which has been provided within the current Marketing Authorization Application. In addition to controls described in the Ph. Eur. monograph and in the CEP, controls of particle size (laser diffraction) and morphology (XRPD) were included in the active substance specifications.

It has been shown that dissolution of the tablets can be affected by changes in physical properties of the product, and potentially by changes in active substance morphology, which can occur following exposure to high humidity. No clear correlation has been defined between polymorphic forms content, water content, tablet hardness and dissolution behaviour/bioavailability of the finished product. Polymorphic form of the active substance as it is and in the finished product is controlled to ensure consistency with the morphology of the drug substance studied in vivo. The manufacturing conditions chosen prevent polymorphic change and tablet physical degradation. The primary packaging, OPA/Aluminium /PVC-Aluminium perforated unit dose blister, provides an effective barrier to environmental humidity and prevents other polymorphic forms formation during storage. However due to concerns over the stability of the unpackaged, sub-divided tablet, the unused half tablet should be discarded. Appropriate storage precautions were included in the SmPC.

Despite this instruction, there is a risk that in practice, the spare half tablet may be retained and administered subsequently. In addition, there is also a concern on the difficulty that elderly and frail patients may have to sub-divide the tablets. In order to address these, the applicant committed to submit a marketing authorization application (MAA) for a 20 mg oral dosage form with an indication in MM in order to eliminate the need to break the 40 mg tablets if a 20 mg dose is prescribed. A variation application should be submitted within 12 months of the first approval of a marketing authorization for the 20 mg oral dosage form to eliminate the score line of the 40 mg tablet (see Risk Management Plan).

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

At the time of the CHMP opinion, there was a number of minor unresolved quality issue related to validation of the method for control of morphology, however this is considered to have no impact on the Benefit/Risk ratio of the product.

2.2.4. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.2.5. Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

The applicant should generate prior to commercialisation satisfactory test method validation for XRPD methodology in line with protocol submitted during procedure.

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.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Cultured ARP-1 multiple myeloma cells (derived from human bone marrow) were shown to undergo extensive apoptosis (>60%) following treatment with a clinically relevant dose of 0.1 µmol/L dexamethasone for 48 hours. This effect was inhibited in transfected ARP-1 cells that over-expressed human bcl-2. In the ARP-1 cells, dexamethasone-induced apoptosis correlated with the inhibition of the DNA binding of NF-κB. The incubation of ARP-1 cells with dexamethasone inhibited NF-κB DNA binding by 5.4%, 30% and 56% after 1, 3 and 6 hours, respectively. Dexamethasone also rapidly increased the expression of the inhibitor of κBα protein (IκBα; an intracellular protein that functions as a primary inhibitor of NF-κB) in bcl-2 over-expressing ARP-1 cells. The inhibition of NF-κB DNA binding was noted to be an early event in the commitment phase of dexamethasone-induced apoptosis. To determine the relationship between persistent NF-κB activity, bcl-2 expression and resistance to

dexamethasone-induced apoptosis, studies were conducted using bcl-2 over-expressing ARP-1 cells and two dexamethasone-resistant human multiple myeloma cell lines which expressed moderate endogenous levels of bcl-2. The resistance to both dexamethasone-induced and spontaneous apoptosis appeared to be associated with the level of bcl-2 expression and maintenance of constitutive NF-κB activation. Similar results were observed in dexamethasone-treated primary multiple myeloma cells derived from patient bone marrow samples. The reduction of NF-κB DNA binding correlated with the patients' sensitivity to dexamethasone; as assessed by the decline in serum or urine paraprotein/tumour specific immunoglobulin levels (Feinman at al., 1999).

The efficiency and kinetics of dexamethasone was evaluated using three well-characterised myeloma cell lines, BCN, NON8 and OPM2 The cell lines were exposed to a constant AUC of dexamethasone, while varying in reverse proportion the time of exposure (6, 16, 23 and 40 hours) and the concentration of dexamethasone in the cell culture medium (510, 191, 127 and 76 nM). The AUC was chosen to correspond to a 40 mg dose of Neofordex calculated according to the results of study CPA 402-11, in order to achieve clinically relevant exposure. The three cell lines, differed in terms of chromosomal rearrangement, pro-oncogene overexpression and relative level of glucocorticoid receptor expression, and were selected as they exhibit different sensitivity to dexamethasone. Cells were assayed for proliferation and apoptosis. For comparison, the same cell lines were exposed to melphalan (a chemotherapy drug used to treat multiple myeloma), again at clinically relevant concentrations. The time of exposure was 6 hours, as a clinical dose is completely cleared in this time.

At constant exposure to dexamethasone, cell survival decreased with increasing time of incubation, even where the dexamethasone concentration in the medium was lower than at shorter incubation times. At 40 hours of exposure to dexamethasone, cell survival was significantly lower than at 6 hours exposure in all three cell lines. After 6 hours of exposure to a very high concentration of dexamethasone, cell survival was influenced only to a negligible degree.

Cell death was induced by dexamethasone during its presence in the medium. After removal of dexamethasone from the medium, cell death was constant over time or showed an apparent decrease due to the proliferation of cells that had not been driven into apoptosis when dexamethasone was present in the culture medium. In contrasts, exposure to melphalan for 6 hours decreased cell survival in a concentration-dependent manner. Melphalan irreversibly induced cell death during a short exposure due to its alkylating activity, resulting in apoptosis peaking 96 hours after exposure. When comparing the percentage of cell death induced by melphalan to that induced by dexamethasone in the same 6 hours of exposure, the difference at 96 hours post-exposure was statistically significant for all cell lines and conditions.

The kinetics of dexamethasone-induced gene expression was investigated using oligonucleotide arrays in dexamethasone-sensitive multiple myeloma (MM.1S) cells (Chauhan et al., 2002). Relatively few genes were upregulated within the first 4 hours of treatment with 10 µmol/L dexamethasone, suggesting that the initial stress response was not mediated through gene induction. Various apoptosis-related genes, including CFLAR (also known as CLARP or Flip), Tis11d, and IκB-α were detected at 2 hours of treatment and maximum levels at 24 hours. Following similar kinetics, anti-apoptotic genes, such as Bcl-xL, were significantly down-regulated in cultured myeloma cells in response to dexamethasone treatment. Dexamethasone treatment of MM.1S cells also produced increased IκB-α protein levels and reduced NF-κB DNA binding.

The kinetics and dose-dependency of dexamethasone-induced apoptosis were further studied in multiple myeloma cells expressing wild-type and mutant glucocorticoid receptors (Sharma and Lichtenstein, 2008). Dexamethasone induced apoptosis in these cell lines in a dose-dependent manner. Substantial caspase-3 (a cysteine aspartic acid protease involved in apoptosis) activity was

detected in cells cultured in the presence of 10 nmol/L or 1 µmol/L dexamethasone for 60 hours. In cells cultured with 1 µM dexamethasone, caspase-3 activity was lower at 48 hours (approximately 20%) than at 60 hours (approximately 40%).

In a study on the effect of dexamethasone on cultured MM.1S cells, dexamethasone induced the release of second mitochondria-derived activator of caspase (Smac; an apoptosis-promoting factor) into the cytosol and activated caspase-9 (Chauhan et al, 2001). Smac was released 12 hours after exposure to 10 µmol/L dexamethasone and increased for up to 48 hours; caspase-9 activation followed similar kinetics. Caspase-8 (a cysteine aspartic acid protease involved in apoptosis) was not activated. Interleukin-6 (IL-6; a growth factor for multiple myeloma) blocked dexamethasone-induced apoptosis in the cultured MM.1S cells and prevented the mitochondrial release of Smac.

Thalidomide, its IMiDs pomalidomide and lenalidomide and dexamethasone induced cell death in MM.1S cells (Hideshima et al., 2000; Hideshima at al., 2001). These IMiDs act directly by inducing apoptosis or G1 growth arrest in myeloma cell lines and in patient multiple myeloma cells that are resistant to dexamethasone, melphalan and doxorubicin. Moreover, thalidomide and the IMiDs enhanced the anti-multiple myeloma activity of dexamethasone. However, in MM.1S cells, the inhibition of DNA synthesis induced by thalidomide and the IMiDs was greatly reduced by IL-6. Apoptotic signalling triggered by dexamethasone (12 hours treatment with 10 µmol/L) and IMiDs was shown to be associated with the activation of protein-tyrosine kinase 2-beta (PTK-β). The activation of PTK-β by IMiDs was also shown in dexamethasone-resistant cell lines.

The growth of MM.1S cells and dexamethasone-resistant multiple myeloma (MM.1R) cell lines was completely inhibited by bortezomib (a marketed proteosome inhibitor used in the treatment of multiple myeloma; Hideshimaet al., 2001). Dexamethasone (0.001 to 0.625 µmol/L) and bortezomib (0.0025 and 0.005 µmol/L) alone inhibited MM.1S cell growth in a dose-dependent manner. The inhibitory effect was additive when cells were cultured in the presence of both dexamethasone and bortezomib combined. In contrast to its inhibitory effect on dexamethasone- and IMiD-induced apoptosis, IL-6 did not abolish the inhibitory effect of bortezomib on multiple myeloma cell growth. In addition, bortezomib blocked NF-κB activation and IL-6 activation in cultured human bone marrow stromal cells (BMSC).

In a further study, carfilzomib (a proteasome inhibitor) induced apoptosis in multiple myeloma cells (cell lines and patient-derived plasma cells) and activated the caspase-8 and caspase-9 pathways (Kuhn et al., 2007). The reduced proliferation observed in cell lines incubated with carfilzomib and dexamethasone combined was synergistically greater than in those treated with the individual drugs alone.

Additional studies have also shown the synergistic effect of dexamethasone and IMiDs or bortezomib combined in the induction of multiple myeloma cell death (Mitsiades at al., 2002). In *in vitro* assays, IMiDs (referred to as IMiD1 and IMiD3) were shown to induce caspase-8, but not caspase-9, activity in cultured myeloma cell lines (MM.1S, OCI-My-5 and S6B45 cells) and bone marrow mononuclear cells derived from multiple myeloma patient cells; whereas dexamethasone activated caspase-9, as mentioned above. IMiD-induced apoptosis was shown to be caspase-8-dependent. The pretreatment of MM.1S cells with IMiDs resulted in increased Fas- (a protein involved in apoptosis) and TRAIL/Apo2L (tumour necrosis factor-related apoptosis-inducing ligand)-induced apoptosis. In these IMiDs treated cells, there was no reduction in bcl-2 protein expression. Pomalidomide treatment alone down-regulated constitutive NF-κB DNA-binding activity in a multiple myeloma cell line. The combination of dexamethasone with pomalidomide totally abolished the NF-κB activity. Pomalidomide also enhanced the induction of myeloma cell death induced by dexamethasone or bortezomib.

Secondary pharmacodynamic studies

No secondary pharmacodynamics studies with dexamethasone were reported (see discussion on non-clinical aspects).

Safety pharmacology programme

No safety pharmacology studies with dexamethasone were reported (see discussion on non-clinical aspects).

Pharmacodynamic drug interactions

No pharmacodynamic drug interactions studies with dexamethasone were reported (see discussion on non-clinical aspects).

2.3.3. Pharmacokinetics

Based on the literature data, the pharmacokinetics of dexamethasone have been studied in mice, rats, dogs and pigs using either [3H] labelled or unlabelled drug. The routes of administration used were intravenous, oral, intramuscular, intraperitoneal and subcutaneous.

Absorption

In rats orally administered 10 mg/kg [^{3}H]-dexamethasone, serum concentrations of the drug were up to 2.3 x 10^{-5} mol/L. Following the intravenous administration of the same dose, the C_{max} was determined to be 4.5x10^{-5} mol/L (Moldenhauer, 1991).

Distribution

In an *in vitro* study using equilibrium dialysis, the binding of dexamethasone to plasma proteins in rat, dog, cow, and human was approximately 85, 73, 74, and 77%, respectively (Peets, 1969). No *in vitro* transport studies with dexamethasone have been reported.

In mice intravenously administered 0.2 mg/kg [^{3}H]-dexamethasone, the highest concentrations of radioactivity at 4 hours post dose were found in the gall bladder and bile (5231 ng/g tissue) and liver (824 ng/g tissue), colon (73 ng/g tissue) and kidney (38 ng/g tissue) (Schinkel, 1995).

Following an intravenous dose of 39.5 µg [^{3}H]-dexamethasone sodium phosphate to rats, the highest percentage of administered radioactivity was found in muscle (35.5%), liver (36.0%) and kidney (4.5%) within 15 minutes post dose. The levels of radioactivity in the tissues declined steadily thereafter (Mizushima, 1982).

Metabolism

The hepatic metabolism of dexamethasone was shown to occur in a two-step process: the addition of oxygen or hydrogen atoms followed by steroid conjugation (glucuronidation and sulphation) (Czock, 2005). Dexamethasone phosphate is rapidly hydrolysed in serum and the metabolism of dexamethasone acetate is expected to be similar.

In an *in vitro* study using mouse, rat, hamster, guinea pig, rabbit, dog and human liver microsome preparations, dexamethasone was shown to be extensively metabolised to 6-hydroxydexamethasone and side-chain cleaved metabolites to various extents.

The inhibitory potency of ketoconazole (a CYP3A4 inhibitor) and glycyrrhetinic acid (a specific inhibitor of 11-dehydrogenase) on dexamethasone metabolism was investigated. 6-Hydroxylation was variable (highest in the hamster), not always the major route of metabolism and its formation was sex-specific

in the rat. The inhibition of 6-hydroxylation by ketoconazole also varied. Cytosolic preparations produced similar profiles in different species with the formation of a metabolite (M5) which was inhibited by glycyrrhetinic acid and tentatively identified as 11-dehydro-side-chain cleaved dexamethasone (11DH-9αF-A). The metabolic profile of dexamethasone in the male rat was most similar to that seen in humans.

Another *in vitro* study using rat liver slices showed that approximately 10% of the recovered drug-related material was associated with conjugated products (Dollery, 1999).

Dexamethasone metabolism in the liver was reported to be slow and limited (Dollery, 1999). In rat urine, unconjugated drug and its metabolites consisted of dexamethasone (48%), 6β-hydroxydexamethasone (30%), 20-dihydrodexamethasone (5%) and 11-ketodexamethasone (approximately 1%). Details of the metabolic pathway of dexamethasone metabolism were not provided.

Excretion

Dexamethasone and its metabolites are excreted in the urine and bile (Hichens, 1974; Van Leeuwen, 2010).

In rats intravenously administered 39.5 µg [^{3}H]-dexamethasone sodium phosphate, the half-life of radioactivity was 2.8 hours (Mizushima, 1982). The cumulative (0-96 hours) urinary and faecal recovery in rats orally dosed [^{3}H]-dexamethasone (1.14 nmol/kg) amounted to 31% and 25% of the administered radioactivity, respectively (Van Leeuwen, 2010). In male rats, intraperitoneally administered 0.23 µmol [1,2-^{3}H]dexamethasone, 74% was excreted within 96 hours; 30.4% in urine and 43.6% in faeces (Van Leeuwen, 2010). Thirty two percent of the radioactivity detected in the urine was associated with a polar metabolite of dexamethasone, considered likely to be 6-hydroxydexamethasone (Rice, 1974; Van Leeuwen, 2010). In rats administered an intramuscular dose of 9 µg/kg [1,2,4-^{3}H]-dexamethasone, 41% and 44% of the administered radioactivity was detected in urine at 0-24 hours and 0-96 hours, respectively (Van Leeuwen, 2010).

In dogs intravenously administered 1 mg/kg dexamethasone alcohol or dexamethasone 21-isonicotinate, the half time of elimination was 120 to 140 minutes (Van Leeuwen, 2010).

In pigs, subcutaneously administered [1,2-^{3}H]-dexamethasone-21-trimethylacetate, less than 1% of total plasma radioactivity was extractable as unchanged [^{3}H]-dexamethasone-21-acetate at 4 hours post dose (Van Leeuwen, 2010). The plasma concentration of dexamethasone was highest (approximately 3 ng/ml) at 4 hours, declining rapidly to approximately 0.5 ng/mL at 24 hours, and slowly thereafter. Measurable amounts of dexamethasone (>0.2 ng/ml) were still present at 5 days post dose.

Pharmacokinetic drug interactions

Dexamethasone is a well-known inducer of CYP3A4. In studies in rats, dexamethasone treatment increased liver and intestinal CYP3A mRNA and protein by 5- and 7-fold, respectively, and intestinal and hepatic P-gp expression by 2- and 3-fold (Lin, 1999). Similar results were observed in other studies (Dexamethasone PK Interaction Report). The induction of CYP3A4 and P-gp is reported to be the basis of a multitude of observed pharmacokinetic drug interactions.

The table below provides the results of studies from the published literature on pharmacokinetic drug-drug interactions with dexamethasone.

Table 5. Dexamethasone Drug Interactions: Literature Data

Molecule	Evidence Source	Detail
Medicinal products with effect on dexamethasone metabolism		
fosaprepitant	*in vivo*, human	Counteracts CYP3A4 & P-gp induction by dex. ↑ 2-fold dex AUC
aprepitant	*in vivo*, human	Counteracts CYP3A4 induction by dex
itraconazole	*in vivo*, human	Inhibition of Dex hydroxylation by CYP3A4, of intestinal efflux through P-gp, ↑ 3-fold dex plasma level, dex t_{max} shortened, longer cortisol suppression
triazolam	*in vivo*, human	No clinically significant effect
ephedrine [1]	*in vivo*, human	↑ i.v. dex metabolic clearance
primidone [2]	*in vivo*, human	↑ oral dexamethasone metabolism
ketoconazole	*in vitro*, human	Inhibition of Dex hydroxylation by CYP3A4, ↑ dex plasma level
Effect of dexamethasone on metabolism of other medicinal product		
dexamethasone	*in vivo*, human	Dex ↓ dex plasma levels due to CYP3A4 induction
cyclophosphamide	*in vivo*, human	Dex ↓ ½ cyclophosphamide AUC
erythromycin	*in vivo*, human	Dex ↑ erythromycin metabolism by CYP3A4 and in *CYP3A5*1* non-carriers
lapatinib	*in vivo*, human	Dex ↑ lapatinib hepatotoxicity likely through induction of CYP3A4
indinavir	*in vivo*, rat	Dex ↓ 3-fold indinavir AUC due to intestinal CYP3A4 induction
ciclosporin	*in vivo*, rat	Dex ↓ ciclosporin plasma levels and bioavailability. Ciclosporin may ↑ dex intracellular uptake
nadolol	*in vivo*, rats	Dex ↓ 1/3 nadolol AUC due to renal P-gp induction
midazolam	*in vivo*, rat	Dex ↓ -80% midazolam AUC due to CYP3A induction
methotrexate	*in vivo*, rat	Dex ↓ ½ methotrexate biliary excretion, potentially due to induction of uptake transporters
verapamil	*in vivo*, rat	Dex counteracts verapamil inhibition of CYP3A & P-gp due to induction of CYP3A & P-gp
docetaxel	*in vivo*, mouse	Dex ↓ docetaxel plasma levels due to induction of CYP3A & P-gp
ivermectin	*in vivo*, bovine	Dex ↓ ivermectin plasma levels
praziquantel [3]	*in vivo*, human	Dex ↓ 50% praziquantel plasma levels
rifabutin [4]	*in vivo*, rat	Dex ↓ 30% i.v. rifabutin (reduction of oral rifabutin not determined), altered metabolite pattern of oral rifabutin due to dex induction of intestinal & hepatic CYP3A

Source: Dexamethasone PK Interaction Report. Dex: dexamethasone; i.v.:intravenous; P-gp: P-glycoprotein/MRP1

[1] additional reference (Brooks, 1977)

[2] additional reference (Hancock, 1978)

[3] additional reference (Vazquez, 1987)

[4] additional reference, (Koudriakova, 1996)

2.3.4. Toxicology

Single dose toxicity

In mice (sex/group not specified) orally, intravenously or intraperitoneally administered dexamethasone sodium phosphate, the LD_{50} values were 6.5, 794 and 577 mg/kg, respectively (which corresponded to 4.9, 603 and 439 mg/kg dexamethasone; Van Leeuwen, 2010). The acute systemic toxicity of dexamethasone was low.

In rats (8 males/group) subcutaneously administered dexamethasone at 6, 15, 30, 60 and 120 mg/kg, deaths occurred at ≥30 mg/kg on Days 6 and 7 post dose and were attributed to infection. Body weight loss (approximately 29.5%) occurred at the highest doses; at the intermediate and lower doses, arrest and retardation of growth, respectively, were observed. By 21 days post dose, body weight gains ranged from 11 to 104 g. At autopsy, multiple small abscesses in the lungs, kidneys, and/or liver were observed in randomly selected animals (Tonelli, 1966).

Repeat dose toxicity

A tabulated summary of the major findings observed after repeated administrations of dexamethasone in rats and dogs is presented in Table 6.

Table 6. Main Findings in Rats and Dogs after Repeated Administration of Dexamethasone

Species/ Strain	Method of Administration (Vehicle/ Formulation)	Duration of Dosing	Doses (mg/kg)	Gender and N per Group	Noteworthy Findings
Rat	Oral	6 days/week, 5 days/week, or 5 days/week respectively for 181-185 days	0.125 mg/kg bw, 0.25 mg/kg bw or 0.4 mg/kg bw	not available	• severe infections; • body-weight gain decreased; • relative kidney weight increased; relative adrenal and thymus weights decreased; • bone marrow: number of neutrophilic forms of leucocytes increased, number of eosinophils decreased
Rats	Subcutaneous	13 weeks	0, 40, or 79 µg/kg bw per day	20 male and 20 female	• ALAT activity and total cholesterol concentrations increased • Plasma corticosteroid levels and hepatic glycogen decreased; adrenal glycogen levels increased. Dose-related reductions in adrenal corticosteroids • adrenal and thymus glands markedly smaller • low body weights
Dogs	Oral	26 weeks	0.2 mg/kg and 0.8 mg/kg bw, per day	4 female beagle dogs	• retro-oesophageal abscesses or gastric ulcers • Infections • Atrophy of the lymphatic organs • adrenal weight decreased
Dogs	Oral	6 weeks	125 µg/kg bw per day	3 male and 2 female dogs	• blood glucose values increased • Relative adrenal weights decreased • Increase 17-ketosteroid excretion in urine
Dogs	Intramuscular	13 weeks	0, 40, or 79 µg/kg bw	3 male and 3 female	• Decreased body-weight gain • ALAT activity increased • Total lipid levels in serum were increased • Increased triglyceride levels in the adrenals and increased liver glycogen • Liver weight increased

ALAT = Alanine aminotransferase
bw = Body weight
N = Numb

Genotoxicity

The genotoxic potential of dexamethasone has been studied in various test systems including *in vitro* assays in bacterial and mammalian cell systems (with and without metabolic activation) and in an *in vivo* micronucleus assay in mice. These studies are summarized in the table below:

Table 7. Results of genotoxicity studies with dexamethasone

Type of test/study ID	Test system	Concentrations or dose range/ Metabolising system	Results
Gene mutations in bacteria (Singh, 1994)	*Salmonella typhimurium* (TA97, TA98, TA100, TA1535)	1 to 10000 µg/plate +/- S9	Negative
Gene mutations in mammalian cells (Lee, 2003)	Mouse lymphoma cells (L5178Y $^{TK+/-}$)	2.5, 5, 10 µg/mL - S9	Negative
Gene mutations in mammalian cells (Singh, 1994)	Human lymphocytes	1 to 100 µg/mL - S9	Negative*
Chromosomal aberrations *in vivo* (Singh, 1994)	Mouse, micronuclei in bone marrow	1000, 5000 or 10000 µg/kg (Intraperitoneal)	Negative*

* = Positive results observed were considered artefacts. Results were therefore negative.

Carcinogenicity

No carcinogenicity studies have been reported (see discussion on non-clinical aspects).

Reproduction toxicity

Reproductive and developmental toxicity studies (fertility and early embryonic development, embryo-fetal development, perinatal and postnatal development and juvenile toxicity studies) have been conducted in mice, rats, rabbits and monkeys.

Table 8. Results of reproductive and developmental toxicity studies with dexamethasone

Study type/ Study ID	Species; Number / group	Route & dose	Dosing period	Major findings
Male fertility (Orazizadeh, 2010)	Mice; 8M	Intraperitoneal 4, 7 or 10 mg/kg/day	7 days	• Epithelial vacuolisation, atrophy and reduction in testicular spermatozoids • Reduced tubular diameter and epithelial height • Reduced spermatogenesis in mice dosed 7 or 10 mg/kg/day neofordex and increased apoptotic index of germ cells
Female fertility (Van Merris, 2007)	N/A	*In vitro* Up to 40 µg/ml	4, 8, 12 days	• 80 µg/ml impaired follicle differentiation and oocyte maturation. • Androgen, estrogen and progestin secretion patterns were impaired at all doses levels

Female fertility (Baldwin, 1974)	Rat; 4 to 12F	Subcutaneous 100, 200, or 500 µg (0.25, 0.5 and 1.25 mg/kg)	Up to 4 days	• Ovulation reduced or inhibited • Delayed ovulation by. • Extended oestrous cycle to 5 days
Female fertility (Rockwell, 2009)	Rat; 86F	Intraperitoneal 1 mg/kg BID	1 or 2 days	• Increased number of oocytes at ovulation • Larger litter size • Reduced pup weights at weaning • Prolonged increase in prolactin levels
Female fertility (Hoffman, 1984)	Rabbit; 4 to 8F	Subcutaneous 3 mg (0.75 mg/kg/day)	GD 5 to 7 or 14	• Reduced number of embryonic implantation and live fetuses • inhibited endometrial phospholipase activity
Embryo-fetal development (Lehmann 1969, Van Leeuwen 2010).	Rat; 20F	Subcutaneous 20, 40 or 79 µg/kg/day	GD 6 to 15	• Single mortality, cause unknown • No weight gain and reduced food consumption during treatment. • Increased mean number of implantations • Dose-related increase in resorption rates • Reduced number of live offspring in the two highest dose groups. • Dose-dependent reduction in litter weight • Retarded ossification of the sternebrae and hydronephrosis
Embryo-fetal development (Druga, 1993, Van Leeuwen, 2010).	Rat; NS	Oral 20, 200, or 1000 µg/kg/day		• Decreased maternal body weight and body-weight gain • Reduced food consumption and thymus involution at 200 and 1000 µg/kg/day. • Increased post-implantation mortality at 1000 µg/kg/day • Reduced fetal weight at 200 and 1000 µg/kg/day. • Reduced umbilical cord length at 200 and 1000 µg/kg/day • Reduced length, thickness, and index of the femur at 1000 µg/kg/day • increased incidence of malformations, in high-dose fetuses (hydrops fetalis, retrognathia, cleft palate, umbilical hernia of variable severity, split sternum, malformed vertebrae, malformed upper limb bones, and micromelia • Thymus hypoplasia at all doses
Embryo-fetal development (LaBorde, 1992; Hansen, 1999)	Rat; NS	Subcutaneous 0.2, 0.4, 0.8 mg/kg	GD 9 to14 or 14 to19	• Reduced maternal food consumption and increased water intake • Dose-related decrease in maternal and fetal body weights • Malformations were noted in the high-dose group on GD 9 to 14 (cleft palate) and on GD 14 to 19 (wavy ribs) • Dose-related stunting in most organs
Embryo-fetal development (Somm, 2012).	Rat; NS	Route not specified 100 mg/kg/day		• Basal hyperglycaemia, decreased glucose tolerance, and pancreatic islet atrophy • Decreased insulin sensitivity
Embryo-fetal development (Kleinhaus, 2010).	Rat; 10F	Intraperitoneal 2 mg/kg	GD 6 to 8	• Increased milk ejection periods during lactation • Offspring showed decreased juvenile social play, blunted acoustic startle reflex, increased pre-pulse inhibition of startle and reduced amphetamine-induced motor activity
Embryo-fetal development	Rat; NS	Subcutaneously	GD 16 to 21	• Decreased corticotropin-releasing factor mRNA in the hypothalamus and disturbed

(Nagano, 2008)		50 µg/kg		the plasma corticosterone response to restraint stress in the offspring at postnatal week (PNW)4 • Increased anxiety-like behaviour in offspring at PNW10 and decreased glucocorticoid receptor expression in the amygdala at PNW7 and PNW10.
Embryo-fetal development (Lehmann, 1969, Van Leeuwen, 2010)	Rabbit; 15F	Subcutaneous 20, 40, or 79 µg/kg/day	GD 6 to 18	• Stationary maternal body weight during the dosing period. • Dose-related increase in resorption rate and number of runts. • Dose-related decrease in fetal weight. • Dose-related increase in the incidence of flexure of the forefeet and of malformations (palatoschisis, gastroschisis, exencephaly, encephalocele and menigocele, anotia, and ectrodactyly) in all treatment groups. • Malformations of the extremities (such as haemibrachia, hypoplasia of tibia and fibula, and acheiria)
Embryo-fetal development (Shah, 1976)	Hamsters, 2 or 4F	Intramuscular 0.5, 1, 2.5, or 5 mg (2.5, 5, 12.5 or 25 mg/kg)	GD 11	• Cleft palate seen at all doses; incidence increased with dose • Frequency of cleft palate was 32% and 75% at the doses of 0.5 and 1 mg, respectively
Embryo-fetal development (Not specified)	Monkey; 6 or 8F	Intramuscular, 0.25 to 4.0 mg/kg/day BID	GD 130 to 175	• Decreased basal levels of maternal oestradiol and cortisol • Abolished prepartum oestrogen and prolactin surges • 71% births were postmature (after Day 167 days) • Fetal death at >0.16 mg/kg/day • Delayed fetal growth and decreased thymus, spleen, and adrenal weights • Decreased brain weight, biparietal and occipitofrontal diameters and head circumference
Poulain, 2012	Human	2, 10, or 50 µM	14 days	• Decreased germ cell density in ovaries • Reduced expression of the pro-survival gene KIT.
Peri and postnatal development (Ferguson, 001)	Rats, 14M	Subcutaneous ; 1.5 mg/kg BID	PND 7	• Decreased body weight beginning at PND 43 until PND 127 (study end) • Reduced brain weights, especially hippocampus, cerebellum, brainstem, and cortical remnant. • Behavioural effects indicative of delayed development, such as longer time to turn and hyperactivity
Peri and postnatal development (Theogaraj, 2005).	Rat, 4 to 8F	Oral 1 µg/ml	GD 16-19 PND 1-7	• Reduced expression of acute annexin 1 (ANXA1), in particular on the outer surface of folliculostellate cells. • Reduced the size of folliculostellate cells • Reduction in corticotroph number and impaired granule margination.

M = Males
F = Females
BID = Twice daily dosing
GD = Gestation Day
PND = Postnatal Day
NS = Number of animals not specified

Toxicokinetic data

No toxicokinetic data has been reported (see discussion on non-clinical aspects).

Local tolerance

No local tolerance studies have been reported (see discussion on non-clinical aspects).

2.3.5. Ecotoxicity / environmental risk assessment

Table 9. Summary of main study results

Substance (INN / Invented Name): dexamethasone			
PBT screening		**Result**	**Conclusion**
Bioaccumulation potential- log K_{ow} of dexamethasone log K_{ow} of dexamethasone acetate	OECD107	 1.83 2.9	Potential PBT No
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$ of dexamethasone, default PEC $_{surfacewater}$ of dexamethasone acetate, default	0.0857 0.0949	µg/L	> 0.01 threshold Yes
PEC $_{surfacewater}$ of dexamethasone, **refined** PEC $_{surfacewater}$ of dexamethasone acetate, **refined**	0.00189 0.00209	µg/L	> 0.01 threshold No

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following point for further investigation to be addressed:

The applicant should revise the ERA to include the proposed transformation study in aquatic sediment systems, consumption data on dexamethasone acetate in relation to its use in multiple myeloma, literature analysis on the known endocrine disruptor activity of dexamethasone in the fish species or submit a protocol for a Fish Full Life-Cycle test for endorsement as appropriate.

2.3.6. Discussion on non-clinical aspects

A series of *in vitro* studies were reported from literature. Dexamethasone has been shown to induce multiple myeloma cell death via a down-regulation of NF-κB activity and an activation of caspase-9 through Smac release. IL-6 and high bcl-2 levels antagonised dexamethasone induced apoptosis. Early apoptotic markers (CFLAR, Tis11d or IκB-α) were rapidly detectable following exposure to dexamethasone. However, prolonged exposure was required to achieve their maximum levels along with increased caspase-3 activation and DNA fragmentation. Dexamethasone also down regulated anti-apoptotic genes and increased IκB-α protein levels. The duration of exposure of three different myeloma cell lines to dexamethasone, and not the concentration of dexamethasone, was shown to be the factor related to decreased cell survival. Dexamethasone-induced apoptosis in myeloma cells was synergistically enhanced by the co-treatment with thalidomide, IMiDs or proteasome inhibitors.

The interaction information in the proposed Neofordex SmPC is derived from the SmPC of the reference medicinal product.

There are no studies to date which have evaluated the potential impact of genetic polymorphisms on the metabolism, safety or efficacy of Neofordex. Polymorphisms in CYPs and transporters may lead to differences in dexamethasone pharmacokinetics and to variability in drug-drug interactions with

dexamethasone. Data on sub-populations carrying known and relevant genetic polymorphism is considered to be important missing information and is noted in the Neofordex Risk Management Plan (see Risk Management Plan).

Glucocorticoids have only weak acute toxicity. No chronic toxicity and carcinogenicity data are available. Genotoxicity findings have been shown to be artefactual. In reproductive toxicity studies in mice, rats, hamsters, rabbits and dogs, dexamethasone has led to embryo-fetal malformations such as increase in cleft palate and skeletal defects; decreases in thymus, spleen and adrenal weight; lung, liver, and kidney abnormalities; and inhibition of growth. Post-natal development assessment of animals treated prenatally presented decreased glucose tolerance and insulin sensitivity, behavioural alterations and decrease in brain and body weight. In males, fertility may be decreased through germ cell apoptosis and spermatogenic defects. Data on female fertility are contradictory (SmPC, section 5.3).

Women should avoid pregnancy during Neofordex treatment. Dexamethasone may cause congenital malformations. Dexamethasone may be used with known teratogens (e.g. thalidomide, lenalidomide, pomalidomide, plerixafor), or with cytotoxic substances which are not recommended in pregnancy. Patients receiving Neofordex in combination with products containing thalidomide, lenalidomide or pomalidomide should adhere to the pregnancy prevention programmes of those products. Reference should be made to all the relevant Summary of Product Characteristics prior to the commencement of any combination treatment for additional information (see section 4.6).

Studies in animals have shown reductions in female fertility. No data on male fertility are available SmPC section 4.6).

2.3.7. Conclusion on the non-clinical aspects

Overall the Non-clinical Overview is considered acceptable to support the clinical use of dexamethasone for the treatment of symptomatic multiple myeloma in combination with other medicinal products.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for 40 mg tablet containing dexamethasone. To support the marketing authorisation application the applicant conducted one single dose bioequivalence study with cross-over design in healthy volunteers under fasting conditions.

No new clinical efficacy and safety data is provided. However, in support of the proposed indication and posology, the applicant has submitted full clinical study reports (one pharmacokinetic study, 4 efficacy and safety studies). The data concerns other formulations of dexamethasone in combination with the centrally authorised products Thalidomide Celgene 50 mg hard capsules, Revlimid 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 25 mg hard capsules (lenalidomide) and Imnovid 1 mg, 2 mg, 3 mg and 4 mg hard capsules (pomalidomide). A number of literature reports are also submitted.

A signed authorisation from Celgene Europe Limited, the Sponsor for the submitted clinical study reports, has been provided.

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

current version is of particular relevance.

GCP

The Clinical trial CPA-402-11 was performed in accordance with GCP as claimed by the applicant.

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

Clinical studies

One bioequivalence study (CPA-402-11) has been submitted.

2.4.2. Pharmacokinetics

Methods

Study design

This was a randomised single-dose, open-label, two-period, two-treatment, two-sequence crossover comparative bioavailability study of Neofordex 40 mg tablets versus Dectancyl 0.5 mg tablets (Sanofi-Aventis France) in healthy volunteers under fasting conditions.

The primary objective was to assess the bioequivalence of half of a tablet of the test product Neofordex 40 mg tablets versus 44 tablets of the reference formulation Dectancyl 0.5 mg tablets (Sanofi-Aventis France) after a single oral dose. A secondary objective was to evaluate the safety and tolerability of these formulations.

This study took place at a single centre. Study drugs were administered at least 10 hours after a supervised overnight fast. The test or reference product was administered with 250 mL of water, according to the randomisation schedule. The test product was administered as half a tablet (cut in half and stored in a labelled bottle prior to administration). The reference product was administered as 44 tablets (counted into a labelled bottle prior to administration). Additional water (in volumes of 100 mL) was provided to facilitate swallowing of the reference tablets in some subjects. The test and reference tablets were swallowed whole and were not chewed or broken. Immediately after administration, the subject's oral cavity and hands were checked to confirm complete medication and fluid intake. Subjects remained fasting for 4 hours post-dose.

Twenty-one (21) blood samples (4 mL each) were collected at time 0 (pre-dose), and at 0.17, 0.33, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.0, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 24 and 36 hours after drug administration in each study period. Actual collection times were recorded. The blood samples were immediately shaken gently and stored in a water/ice bath at +4±2°C until centrifugation within 10 minutes after collection. The plasma samples were transferred into labelled polypropylene tubes in two splits, then capped and frozen on dry ice. The samples were stored at the study site's bioanalytical laboratory in a freezer with continuously controlled temperature of -25°C (range -20°C to -35°C) until shipment in dry ice to the analytical facility. Plasma concentrations of the parent drug dexamethasone were determined in plasma using a validated HPLC-MS/MS method. The bioassay was blinded regarding the treatment sequences. The washout period was at least 12 days.

Test and reference products

The test product Neofordex 40 mg Tablets contains 40 mg of dexamethasone base corresponding to 44.3 mg of dexamethasone acetate. Dectancyl 0.5 mg tablets contain 0.5 mg of dexamethasone acetate corresponding to 0.451 mg of dexamethasone base. Consequently the molar dose of the half tablet of Neofordex 40 mg Tablets represents 100.81% of the molar dose of 44 tablets of the reference product Dectancyl 0.5 mg tablets.

Table 10. Comparison of test and reference products

	Test product	**Reference product**
Product	Neofordex 40 mg tablets (Laboratoires CTRS, France)	Dectancyl 0.5 mg tablets (Sanofi-Aventis France, France) from French market (MA number: 34009 302 853-6 7)
Strength	44.3 mg of dexamethasone acetate equivalent to 40 mg of dexamethasone base	0.5 mg of dexamethasone acetate equivalent to 0.451 mg of dexamethasone base
Dose	20 mg of dexamethasone (as one half of the test tablet)	19.86 mg of dexamethasone as 44 reference tablets
Batch number	9433002	060 and 061
Batch size	134,520	N/A
Assay (content of dexamethasone acetate)	43.9 mg/tablet	060: 0.50 mg/tablet 061: 0.49 mg/tablet
Manufacturing date	09/2010	N/A
Expiry date	06/2013	060: 05/2013 061: 05/2014

Population studied

Twenty-four healthy volunteers (12 male, 12 female), aged 19-55, body mass index (BMI) 20.6 – 29.7 kg/m^2 were enrolled and gave informed consent. All subjects were Caucasian. Subjects were screened for eligibility within 28 days prior to dosing, according to standard inclusion and exclusion criteria for this type of study. All subjects completed the study and were included in the pharmacokinetic (PK) and statistical analysis. Subjects were non-smokers or mild smokers (no more than 9 cigarettes, 2 cigars or 2 pipes per day). Smoking and alcohol were prohibited for 48 hours prior to and 36 hours after drug administration. Subjects were confined at least 11.5 hours before and 24 hours after dosing.

Analytical methods

Content of dexamethasone in plasma was determined by liquid/liquid extraction of dexamethasone from plasma, followed by HPLC separation with mass spectrometric detection (LC–MS/MS). Flumethasone was used as an internal standard. Chromatographic separation was performed with a Zorbax SB C18 column with isocratic elution of purified water containing 0.5% of acetic acid / ethanol (67:33 v/v). The method has been demonstrated to be linear between the lower limit of quantification (LLOQ) of 1.00 ng/ml and the upper limit of quantification (ULOQ) of 250 ng/ml.

Bioavailability study plasma samples were stored at -20°C until analysis which was performed from 12 March to 30 March 2012, a storage period that is covered by stability data.

The concentrations of dexamethasone were determined in 1008 samples from 1 clinical site. All requirements for study acceptance were fulfilled. More than 67% of incurred samples reanalysed were within ± 20%. The calibration curve covered the expected unknown sample concentration range except for 10 samples which were re-assayed after a 2-fold dilution. The samples have been stored at approximately -20°C in a freezer of the test facility; no plasma sample underwent more than 3 freeze/thaw cycles. Acceptable stability data to cover these conditions has been showed in a method validation report, which also provided appropriate assurance of selectivity, carry-over, matrix effect, linearity, extraction recovery, within- and between-run accuracy and precision and LLOQ.

Pharmacokinetic variables

The primary PK parameters were AUC_{0-36} and C_{max}. T_{max}, $AUC_{0-\infty}$, residual area, λ_z, and half-life were also calculated. Actual sampling time-points were used in the PK analysis. A non-compartmental method was used. The validated program PhoenixTM WinNonlin version 6.1 (Pharsight Corporation, St. Louis, MO, USA) was used for the calculation of pharmacokinetic parameters.

Statistical methods

The 90% bioequivalence criteria were pre-defined as 80.00-125.00% for both AUC_{0-36} and C_{max}.

The treatment sequences were generated using a computer random number generator (SAS version 9.2). Subjects were assigned to the treatment sequence in a strict chronological order.

The 90% confidence intervals for the ratio test/reference of the geometric least square means were used for the bioequivalence assessment based on logarithmically-transformed data of C_{max} and AUC_{0-36} in all evaluable subjects. Comparisons between treatments were done using the linear mixed model, where effects of treatment, period and sequence are taken as fixed and the effect of subjects nested within sequence as random. This model was applied using the procedure MIXED implemented in the statistical package SAS version 9.2 or higher. The T_{max} was analyzed without ln-transformation using the non-parametric Wilcoxon's test.

Results

The Pharmacokinetic parameters for dexamethasone are presented in tables 11 and 12 and figure 2.

Table 11. Pharmacokinetic parameters for dexamethasone (non-transformed values)

Pharmacokinetic parameter	Test (n=24)		Reference (n=24)	
	Arithmetic mean	SD (CV%)	Arithmetic mean	SD (CV%)
$AUC_{(0-36)}$ [µg.h/L]	1116.86	346.20 (31.00)	1191.91	403.78 (33.88)
$AUC_{(0-\infty)}$ [µg.h/L]	1140.30	366.43 (32.13)	1213.52	423.72 (34.92)
C_{max} [µg/L]	125.93	23.06 (18.31)	213.57	54.04 (25.30)
T_{max}* [h]	3.0 (1.8-8.0)		0.9 (0.5-5.0)	
Half-life [h]	4.60	1.26	3.97	1.17

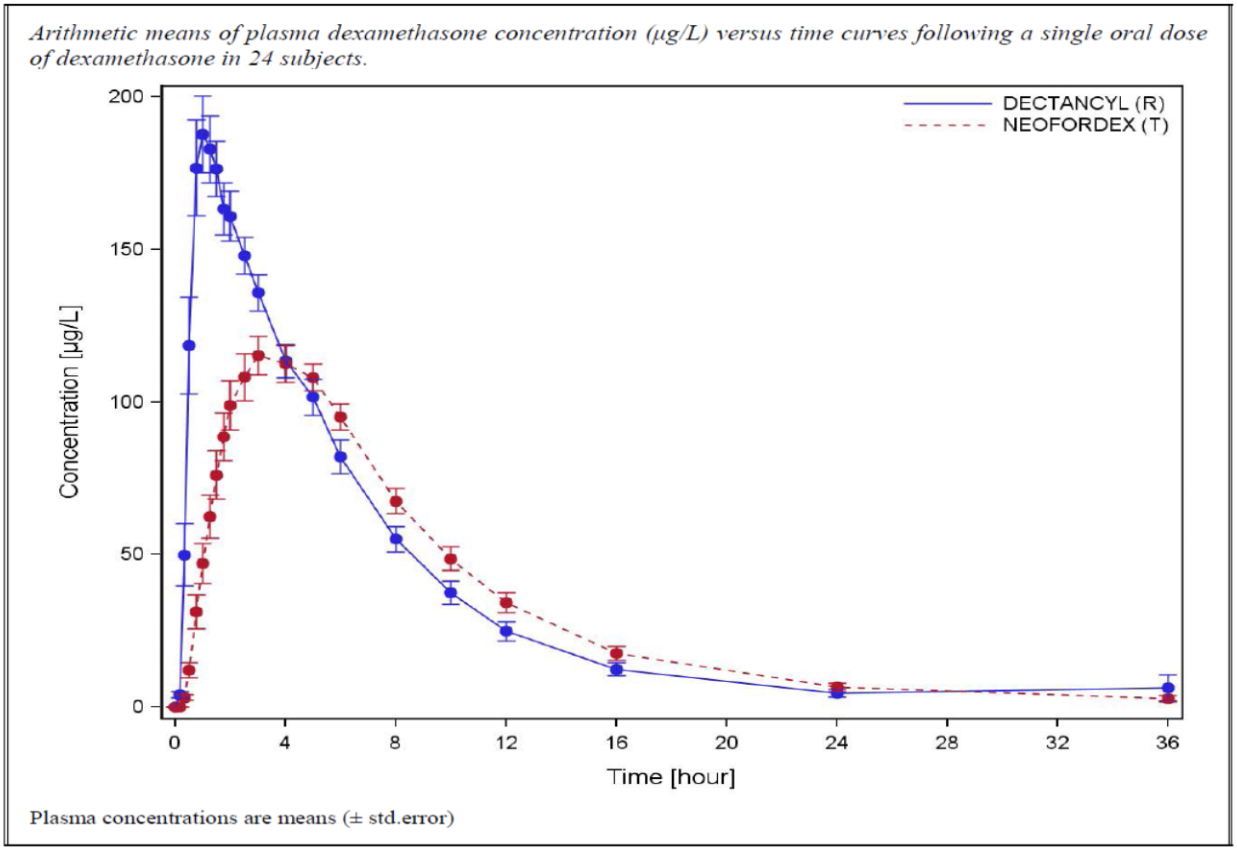
AUC_{0-36}	area under the plasma concentration-time curve from time zero to 36 hours
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
C_{max}	maximum plasma concentration

Pharmacokinetic	Test (n=24)	Reference (n=24)
T_{max}	time for maximum concentration (* median, range)	

Table 12. Statistical analysis for dexamethasone (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio [%] Test/Reference	Confidence Intervals [%]
$AUC_{(0-36)}$	94.17	89.08 - 99.56
$AUC_{(0-\infty)}$	94.47	89.26 – 99.99
C_{max}	59.75	56.32 – 63.38

Figure 2. Arithmetic means of plasma dexamethasone concentration versus time curves



An additional sub-group analysis, based on subjects who drank 350mL of water when ingesting the reference product (n=9) vs. subjects who drank 250mL of water (n=15) has been provided. The results are presented in Table 6 below.

Table 13. Statistical analysis for dexamethasone (ln-transformed values): subgroups based on volume of ingested water

Pharmacokinetic parameter	Geometric Mean Ratio [%] Test/Reference	Confidence Intervals [%]
Subgroup ingesting 250mL (n=15)		
$AUC_{(0-36)}$	92.93	87.40 – 98.82
$AUC_{(0-\infty)}$	93.40	87.73 – 99.44
C_{max}	58.58	53.13 – 64.58
Subgroup ingesting 350mL (n=9)		
$AUC_{(0-36)}$	99.07	86.23 – 113.82
$AUC_{(0-\infty)}$	94.47	86.51 – 114.83
C_{max}	58.95	52.98 – 65.60

Sampling around Tmax occurred less frequently for the test product compared to the reference product, due to a longer actual Tmax. However, based on the concentration-time profiles derived, it is judged that more frequent sampling around 3 hours would not have significantly altered the conclusion regarding AUC0-36.

Conclusions

The bioavailability of Neofordex 40 mg tablets is comparable to that of the reference product Dectancyl 0.5 mg tablets (Sanofi-Aventis France, France), as measured by AUC0-36. The Cmax of Neofordex 40 mg tablets is significantly lower than that of Dectancyl 0.5 mg tablets. The applicant has provided relevant non-clinical *in vitro* data to support the low relevance of the Cmax value in the clinical efficacy of dexamethasone in multiple myeloma treatment (see Section 2.3.2 Primary pharmacodynamic studies). The extrapolation of this non-clinical data to the clinical situation is considered acceptable.

The results of study CPA 402-11 with 40 mg formulation (half tablet) may be extrapolated to 40 mg (whole tablet), according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1, section 4.1.6.

Pharmacokinetics in target population

Study CC-5013-MM-017-PK

The applicant submitted the following clinical study report, with consent from the sponsor (Celgene Europe Limited): 'A multicentre, phase I study to determine the maximum tolerated dose, safety, pharmacokinetics and efficacy of lenalidomide with and without dexamethasone in Japanese subjects with previously treated multiple myeloma.'

Phamacokinetic parameters of dexamethasone 40 mg, in combination with lenalidomide, were derived, for 6 patients with previously treated multiple myeloma, during days 1-12 of cycle 1. This cohort received lenalidomide at 25 mg QD on Days 1 and 3-12 and dexamethasone at 40 mg QD on Days 2-4 and 9-12. Subjects in the Combination Treatment Cohort did not receive dexamethasone on Day 1 and lenalidomide on Day 2 to allow the evaluation of the single dose pharmacokinetics of lenalidomide and dexamethasone on Day 1 and Day 2, respectively. Serial sampling of blood was done on days 2 and 12 for dexamethasone analysis, following an overnight fast. The dexamethasone formulation, supplied by the sponsor, was 4 mg tablets.

Table 14: Pharmacokinetics of dexamethasone when administered alone or in combination with lenalidomide in Japanese subjects with multiple myeloma

Parameters	Combination Treatment	
	Dex 40 mg alone	Len 25 mg + Dex 40 mg
	Day 2 (N = 6)	Day 12 (N = 6)
T_{max} (h)	2.49 (1.00-4.00)	1.75 (0.47-3.07)
C_{max} (ng/mL)	499 (33.0)	523 (33.9)
AUC_t (ng•h/mL)	3528 (38.4)	2633 (44.5)
AUC_τ (ng•h/mL)	3526 (38.3)	2687 (43.0)
AUC_∞ (ng•h/mL)	3661 (43.8)	NA
$t_{1/2}$ (h)	4.24 (31.9)	3.85 (32.3)
CL/F (mL/min)	182 (43.8)	248 (43.0)
Vz/F (L)	66.9 (23.3)	82.7 (21.3)
AR(C_{max})	NA	1.05 (18.7)
AR(AUC_τ)	NA	0.762 (16.2)

Geometric mean (CV%) data are presented for all parameters except that Median (min – max) are presented for T_{max}. CV% = coefficient of variation for geometric mean; Dex = dexamethasone; Len = lenalidomide; NA = not applicable.

Source: Table 14.2.1.12 and Table 14.2.1.13

2.4.3. Pharmacodynamics

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

2.4.4. Clinical efficacy

The applicant has submitted literature reports. No clinical efficacy studies have been conducted using Neofordex 40 mg Tablets.

The following table summarises the submitted literature reports for the first-line treatment of MM.

Table 15: Overview of studies for first line treatment of multiple myeloma

Active substance combination	Study	Study Design	Objective	ASCT eligibility	Treatment arms	N
LenDex	Rajkumar 2010	Phase III, multicentre, open-label, randomised	Efficacy and safety	Yes	Len plus Low-dose Dex[a] Len plus High-dose Dex[b]	445
	Zonder 2010	Phase III, multicentre, double blind, randomised	Efficacy and safety	No	LenDex PlaceboDex	192
BorDex	Harousseau 2010	Phase III, multicentre, open-label, randomised	Efficacy and safety	Yes	VAD induction VAD induction, DCEP consolidation BorDex induction BorDex induction, DCEP consolidation	482
ThalDex	THAL-MM-003	Phase III, multicentre, double-blind, randomised	Long term efficacy	No	ThalDex PlaceboDex	466
	Cavo 2010	Phase III, multicenter, open-label, randomised	Efficacy and safety	Yes	ThalDex induction and consolidation BTD induction and consolidation	474
BTD	Cavo 2010	See description under ThalDex combination				
	van Rhee 2010	Phase II, open-label, non-randomised, single arm	Efficacy and impact of Bor, Thal, and Dex cumulative dosing and PMDD on outcome	Yes	BTD-PACE induction and consolidation	303
BLD	Richardson 2010	Phase I/II, multicentre, open-label, non-randomised, single arm	MTD, efficacy, and safety	Yes and No	BLD	66
VAD	Alexanian 1992	Phase II like design, non-randomised, single arm	Safety and efficacy of Dex vs. VAD[c]	NA	Dex	112
	Harousseau 2010	See description under BorDex combination				

Source: (Alexanian et al. 1992; Barlogie et al. 2007; Cavo et al. 2010; Harousseau et al. 2010; Rajkumar et al. 2010; Richardson et al. 2010; van Rhee et al. 2010; Zonder et al. 2010), Method section; THAL-MM-003 CSR synopsis.

[a] Low-dose dexamethasone consisted of 40 mg/day once a week, in 28-day cycles.
[b] High-dose dexamethasone consisted of 40 mg/day on Days 1 to 4, 9 to 12, and 17 to 20, in 28-day cycles.
[c] VAD results were from a previous study by Alexanian et al. (Alexanian et al. 1990).
ASCT: autologous stem cell transplantation, Bor: bortezomib, BorDex: bortezomib plus dexamethasone, BTD: bortezomib, thalidomide, and dexamethasone, BTD-PACE: bortezomib, thalidomide, and dexamethasone plus cisplatin, doxorubicin, cyclophosphamide, and etoposide, DCEP: dexamethasone, cyclophosphamide, etoposide, and cisplatin, Dex: dexamethasone, Len: lenalidomide, LenDex: lenalidomide plus dexamethasone, MTD: maximum tolerated dose, N: total number of patients, NA: not applicable, PACE: cisplatin, doxorubicin, cyclophosphamide, and etoposide, PlaceboDex: placebo plus dexamethasone, PMDD: premature drug discontinuation, Thal: thalidomide, ThalDex: thalidomide plus dexamethasone, VAD: vincristine, doxorubicin, dexamethasone.

Rajkumar 2010: Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial.

Patients were eligible if they had previously untreated symptomatic multiple myeloma, bone marrow plasmacytosis (≥10% plasma cells or sheets of plasma cells) or a biopsy proven plasmacytoma, and measurable disease defined as serum monoclonal protein of more than 10 g/L or urine monoclonal protein of ≥ 0.2 g per day. Patients were enrolled between 2004 and 2006.

The study was open-label. Patients were randomly assigned 1:1 to receive lenalidomide + high dose dexamethasone or lenalidomide + low-dose dexamethasone. The high dose regimen consisted of oral lenalidomide 25 mg daily days 1-21 plus oral dexamethasone 40 mg daily on days 1-4, 9-12, and 17-20 of each 28 day cycle. The low dose regimen differed in that dexamethasone was given only on days 1, 8, 15 and 22. After the first 4 cycles, patients could discontinue therapy to pursue stem cell transplantation (or other treatment options) or continue with study treatment until progression. Bisphosphonate treatment and thromboprophylaxis was also recommended. If patients progressed or did not respond during the first 4 treatment cycles, thalidomide was substituted for lenalidomide.

The primary purpose of this study was to determine if lenalidomide plus low-dose dexamethasone had a response rate that was not inferior to lenalidomide plus high-dose dexamethasone, while reducing toxicity.

The primary endpoint was overall response rate (ORR) in the first 4 cycles among eligible patients. Additional endpoints included best overall response, time to progression (TTP), progression-free survival (PFS), and overall survival (OS). The response and progression criteria used were standard

European Group for Blood and Bone Marrow Transplant (Bladé) criteria. Patients were also classified as having a very good partial response with the International Myeloma Working Group response criteria.

223 patients were randomly assigned to receive lenalidomide plus high-dose dexamethasone and 222 to receive lenalidomide plus low-dose dexamethasone. 214 patients in the high-dose group were eligible for analysis, compared to 208 in the low dose group. Because the study was designed as an induction trial and patients were allowed to go off-study to pursue autologous stem-cell transplantation, 167 patients interrupted or stopped treatment to have stem-cell harvest. Of these patients, 163 (98%) were successful and four (2%) were unsuccessful.

67% of patients in the high-dose group had bone disease at baseline compared with 57% in the low-dose group. The groups were balanced with regard to age (median 66 years in high dose group vs. 65 years in low dose group), gender, race, stage and performance status.

169 (79%) of 214 patients receiving high-dose therapy and 142 (68%) of 205 patients on low-dose therapy had complete or partial response within four cycles (odds ratio 1·75, 80% CI 1·30–2·32; p=0·008). However, at the second interim analysis at 1 year, OS was 96% (95% CI 94–99%) in the low-dose dexamethasone group compared with 87% (82–92%) in the high-dose group (p=0·0002). As a result, the trial was stopped and patients on high-dose therapy were crossed over to low-dose therapy.

52% of patients on the high-dose regimen had grade 3 or worse toxic effects in the first 4 months, compared with 35% on the low-dose regimen for whom toxicity data were available (p=0·0001). The three most common grade 3 or higher toxicities, all more common in the high dose group, were: deep-vein thrombosis, infections including pneumonia, and fatigue. Twelve patients on high dose treatment died in the first 4 months, compared to one on low dose.

Zonder 2010: Lenalidomide and high-dose dexamethasone compared with dexamethasone as initial therapy for multiple myeloma: a randomized Southwest Oncology Group trial (S0232).

The study included patients with untreated multiple myeloma who were ineligible or who had opted not to have bone marrow transplantation. Patients had to have symptomatic disease with measurable M-protein.

Patients were randomised 1:1 to either lenalidomide and dexamethasone or dexamethasone and placebo. Induction therapy consisted of three 35 day cycles of dexamethasone on days 1-4, 9-12 and 17-20 plus lenalidomide 25 mg daily for 28 days or placebo. Maintenance therapy consisted of dexamethasone 40 mg daily on days 1-4 and 15-18 plus lenalidomide 25 mg daily for 21 days (or placebo) in repeating 28 day cycles. Both treatment arms were continued until disease progression or unacceptable toxicity. Upon disease progression, patients on dexamethasone alone could cross over to open-label lenalidomide +dexamethasone.

The stated primary objective was to compare PFS between the treatment groups. Other endpoints were ORR, OS and toxicity.

The Data and Safety Monitoring Committee recommended early study closure, after enrolment of 198 patients. This was based on inferior efficacy of dexamethasone only, and concern over the safety of lenalidomide in conjunction with dexamethasone in excess of 40 mg weekly.

The combination of lenalidomide and dexamethasone was associated with improved 1 year PFS, 3 year PFS, and ORR (partial or better) compared to dexamethasone alone. There was a trend towards improved OS measured at 1, 2 and 3 years survival for lenalidomide and dexamethasone compared to dexamethasone alone. However this was not statistically significant.

Harousseau 2010 : Bortezomib Plus Dexamethasone Is Superior to Vincristine Plus Doxorubicin Plus Dexamethasone As Induction Treatment Prior to Autologous Stem-Cell Transplantation in Newly Diagnosed Multiple Myeloma: Results of the IFM 2005-01 Phase III Trial.

Patients less than 65 years with untreated symptomatic multiple myeloma, and measurable paraprotein in serum (>10g/L) or urine (>0.2g/24 hours), were enrolled.

The study was open-label. Patients were randomised (1:1:1:1) to receive:

- vincristine + doxorubicin + dexamethasone (VAD)
- VAD + dexamethasone, cyclophosphamide, etoposide and cisplatin (DCEP) consolidation
- bortezomib plus dexamethasone (bordex)
- bordex plus DCEP consolidation

Dexamethasone was given as a 40 mg daily oral dose. VAD was given as four 28 day cycles (dexamethasone days 1-4 all cycles, days 9-12 and 17-20 cycles 1 and 2). Bordex was given as four 21-day cycles (dexamethasone days 1-4 all cycles, days 9-12 cycles 1 and 2). DCEP was given as two 4-week cycles (dexamethasone days 1-4).

The objective was to compare the efficacy and safety of VAD and bordex as induction therapy before HDT-ASCT.

The primary endpoint was post induction CR/nCR rate. Secondary end points included post induction ORR, CR/nCR rate with and without DCEP consolidation, CR/nCR and at least VGPR rates post first transplantation, proportions of patients requiring a second transplantation, and safety and toxicity of induction. Response assessments were confirmed by an independent review committee.

482 patients were randomly assigned to the 4 treatment arms. No significant differences were observed between groups. Median age in all groups was 57 years.

Post-induction CR/nCR rate was significantly higher following induction with bordex versus VAD (14.8% v 6.4%; P = 0.004). Similarly, at least VGPR (37.7% v 15.1%; P < .001) and overall response rates (78.5% v 62.8%) were significantly higher. The addition of DCEP did not improve response rates. Post first transplantation, Cr/nCR and at least VGPR rates remained significantly higher with bordex. Median progression-free survival (PFS) was 36.0 months for bordex versus 29.7 months for VAD (P=0.064). Respective 3-year survival rates were 81.4% and 77.4%.

Haematological toxicity grades 3 and 4 were more common in the VAD group, including seven deaths (2.9%) compared to none in the bortezomib plus dexamethasone group. During induction, consolidation, and first transplantation, peripheral neuropathy was reported in 32.2% and 52.7% of patients who received VAD and bordex respectively.

THAL-MM-003*:* A multicenter, randomized, parallel-group, double blind, placebo-controlled study of combination thalidomide plus dexamethasone therapy versus dexamethasone therapy alone as induction therapy for previously untreated subjects with multiple myeloma.

The applicant has provided a full clinical study report (dated 15 December 2006), with the consent of the sponsor (Celgene Europe Limited).

Subjects were > 18 years, with a diagnosis of active multiple myeloma (Durie-Salmon Stage II or III) not previously treated with anti-myeloma systemic therapy, and measurable levels of myeloma paraprotein in serum (≥ 1.0 g/dL) or urine (≥ 0.2 g/24-hour). 436 subjects were planned.

Study treatment was randomly allocated 1:1. Treatments were given in 28-day cycles. Thalidomide (or placebo) was given as 50 mg capsules to be taken daily orally at bedtime. If tolerated with ≤ Grade 2 toxicities, this dose could be escalated to a maximum of 200mg once daily. The dexathasone dose was 40 mg orally per day. Dexamethasone was to be taken on Days 1 to 4, 9 to 12, and 17 to 20 of each cycle for cycles 1 to 4; and starting at cycle 5, only for the first 4 days of each cycle. Subjects experiencing toxicities related to dexamethasone dosing could have their dose modified to 40 mg once daily for 4 days every 2 weeks, then 4 days every 4 weeks, and finally 20 mg daily for 4 days every 4 weeks. Subjects were treated with bisphosphonates. The treatment regimen was continued until disease progression.

The primary objective was to compare the efficacy of a combination of oral thalidomide plus oral dexamethasone (thaldex) with oral dexamethasone alone as induction therapy for subjects with active multiple myeloma.

The primary efficacy endpoint was time to disease progression as determined by the Response Review Committee based on Bladé criteria. Secondary endpoints were PFS, response rate, duration of response, time to first symptomatic skeletal-related event, and OS.

Subjects were stratified at time of randomisation by age, ECOG performance status score, and baseline serum beta-2 microglobulin (β 2M) level.

In total, 470 subjects were randomised. A total of 431 (91.7%) subjects met all eligibility criteria, were evaluated after at least 1 dose of study drug, and had no important protocol deviations. These subjects comprised the efficacy-evaluable population.

The median age was 65 years in the thadex group compared to 66 years in the placebo/dexamethasone group. Other characteristics were also well-matched between treatment groups.

The median TTP was 97.7 weeks in the thaldex group compared with 28.3 weeks in the placebo/dexamethasone treatment group (HR 0.43, 95% CI 0.32-0.58, p<0.0001). The median PFS was 64.4 weeks in the thaldex group compared with 28.0 weeks in the placebo/dexamethasone group (HR 0.50, 95% CI 0.38 to 0.64, p<0.0001). The overall response, defined as the highest response achieved during the treatment phase that was either a complete or partial response, was higher in the thaldex group (63.0% v. 46.0%; p=0.0003). 7.7% subjects in the thaldex group exhibited a complete response compared with 2.6% subjects in the placebo/dexamethasone treatment group. The thaldex group had a statistically significant prolongation of myeloma response compared with the placebo/dexamethasone group (HR 0.41, 95% CI 0.29 to 0.59, p<0.0001). The median overall survival time from randomization was not reached in the thaldex group and was 128.6 weeks in the placebo/dexamethasone group.

Cavo 2010: Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation (ASCT) in newly diagnosed multiple myeloma: a randomised phase 3 study.

Patients were aged 18-65 with previously untreated symptomatic multiple myeloma were enrolled.

The study was open-label. Patients were randomised 1:1 to receive three 21-day cycles of thalidomide (100mg daily for first 14 days, then 200mg daily) plus dexamethasone (40 mg daily on 8 of the first 12 days) (TD), either alone or in combination with bortezomib (1.3mg/m^2 on days 1,4,8 and 11) (VTD). Randomisation was stratified by disease stage. After double ASCT, patients received two 35-day cycles of their assigned drug regimen, VTD or TD, as consolidation therapy. Between the two ASCT procedures, all patients received 100mg thalidomide daily, and dexamethasone 40 mg daily on days 1-4, every 28 days. Following the consolidation therapy, all patients received maintenance therapy with

dexamethasone 40 mg days 1-4, every 28 days. There was no planned dose reduction of the dexamethasone component.

The primary objective was to assess the efficacy and safety of the addition of bortezomib to thalidomide and dexamethadone (VTD) versus TD alone as induction therapy before, and consolidation therapy after, double ASCT in newly diagnosed multiple myeloma.

The primary endpoint was the rate of complete or near complete response to induction therapy. The analysis was intention to treat. Secondary endpoints were rate of complete plus near complete response to double transplantation and subsequent consolidation therapy, time to progression or relapse, PFS, OS, and safety. Outcomes were independently assessed.

The median ages were 58 years and 57 years for the VTD and TD arms respectively. Other baseline characteristics were balanced between treatment arms. 480 patients were enrolled and randomised.

After induction therapy, complete or near complete response was achieved in 31% (95% CI 25·0–36·8) receiving VTD, and 11% (95% CI 7·3–15·4) on TD ($p<0·0001$). The secondary outcomes were all in line with the primary outcome. No difference in overall survival was detected.

Van Rhee 2010: Total Therapy 3 for multiple myeloma: prognostic implications of cumulative dosing and premature discontinuation of VTD maintenance components, bortezomib, thalidomide, and dexamethasone, relevant to all phases of therapy.

303 newly diagnosed patients with symptomatic or progressive multiple myeloma were enrolled. Ages are not specified in this publication.

Patients received Total Therapy 3 (TT3), consisting of 2 cycles of VTD-PACE (bortezomib, thalidomide, dexamethasone; 4-day continuous infusions of cisplatin, doxorubicin, cyclophosphamide, etoposide) as induction before and, at reduced doses as consolidation after, melphalan-based tandem transplantation. Thalidomide and dexamethasone were given at 50 mg/day and 20 mg/day for 4 days every 28 days to “bridge” drug-free intervals between induction cycles, whereas thalidomide dosing was 100 mg/day with dexamethasone 20 mg/day for 4 days every 28 days between transplantations and consolidation cycles. Maintenance therapy comprised VTD in year 1 and TD in years 2 and 3.

Endpoints included complete response (Bladé), complete response duration, event-free survival (EFS), overall survival, time to next treatment (TNT) and post-relapse survival (PRS). The impact of cumulative dosing of VTD components on OS, EFS, TNT and PRS was also investigated.

Gene expression profiling (GEP) of CD138-enriched plasma cells was performed in a subset of 275 patients.

The 5-year estimates of OS and EFS were 72% and 69%, respectively. Of the 62% of patients achieving CR, 82% retained this status 5 years later.

Regarding VTD dosing, OS and EFS were longer when higher doses had been delivered of all 3 agents during induction, of V and D in consolidation, and of D in maintenance. Given the prognostic implications of cumulative dosing of dexamethasone throughout all phases of therapy, the authors investigated whether the expression level of its target, glucocorticoid receptor gene NR3C1, impacted clinical outcome. NR3C1 top-tertile expression levels were linked to longer and bottom-tertile levels to shorter OS and EFS. Dexamethasone dosing in induction extended OS and EFS only when NR3C1 expression was low.

Premature drug discontinuation of bortezomib, thalidomide or dexamethasone conferred shorter EFS, OS and TNT in univariate models, of which bortezomib retained independent significance for OS and both thalidomide and dexamethasone for TNT.

Richardson 2010: Lenalidomide, bortezomib and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma.

Sixty-six patients were enrolled: all were over 18 years, with previously untreated symptomatic multiple myeloma. The median age was 58 years (59 years for the phase 2 population).

Patients received 3-week cycles (n =8) of bortezomib 1.0 or 1.3 mg/m^2 (days 1, 4, 8, 11), lenalidomide 15 to 25 mg (days 1-14), and dexamethasone on days 1, 2, 4, 5, 8, 9, 11, 12 (at a dose of 40 mg daily cycles 1-4 and 20 mg daily cycles 5-8). Responding patients proceeded to maintenance or transplantation. Phase 2 dosing was determined to be bortezomib 1.3 mg/m2, lenalidomide 25 mg, and dexamethasone 20 mg.

The primary endpoints were to determine the MTD of bortezomib, lenalidomide and dexamethasone (phase 1) and to evaluate the response rate (partial response or better) to the combination (phase 2). Secondary end points included complete plus near-complete response (CR+ nCR) rate, duration of response (DOR), PFS, OS, and toxicity. The rate of very good partial response (VGPR) or better was also determined.

Two patients in dose level 4 (including dexamethasone 40 mg or 20mg on specified days) experienced DLT, specifically grade 3 hyperglycemia and grade 3 alanine transaminase elevation, both attributable to dexamethasone by the investigator. An additional dose level 4M (including dexamethasone 20 mg or 10 mg) was investigated, enrolling 6 patients per protocol; no further DLT was reported in these initial 6 patients enrolled in phase 1 nor in the subsequent expanded phase 1 cohort, and 4M was established as the MTD.

The rate of partial response was 100% in both the phase 2 population and overall, with 74% and 67% achieving at least a very good partial response, respectively.

Alexanian 1992: Primary Dexamethasone Treatment of Multiple Myeloma

This was a longitudinal single-arm study. 112 consecutive previously untreated symptomatic multiple myeloma patients were enrolled between 1989 and 1991. The dexamethasone dose regimen was 20 mg/m^2 each morning on days 1-4, 9-12, and 17-20. After a 14-day rest, the treatment was repeated with downward dose adjustments for side effects.

Median age was 60 years. The overall response rate was 43% (criteria based on a 75% or greater reduction of calculated tumour mass). Response and survival data were compared with those of a VAD regimen studied immediately before the dexamethasone program in 177 previously untreated patients. In the VAD study the overall response rate was stated to be 55%. All patients responding to VAD or dexamethasone showed a tumour halving time of 3.2 months or less, and a remission was confirmed in 80% of patients within 2 months.

The following table summarises the submitted literature reports for the treatment of relapsed/refractory MM.

Table 16. Overview of Studies for Treatment of Relapsed / Refractory Multiple Myeloma

Active substance combination	Study	Study Design	Objective	Treatment arms	N
LenDex	CC-5013 MM-009	Phase III, multicentre, double-blind, randomised	Efficacy and safety	LenDex PlaceboDex	353
	CC-5013 MM-010	Phase III, multicentre, double-blind, randomised	Efficacy and safety	LenDex PlaceboDex	351
PomDex	CC-4047-MM-003	Phase III, multicentre, open-label, randomised	Efficacy and safety	PomDex LD Dex HD	
BorDex	Kobayashi 2010	Retrospective, multicentre	Efficacy, safety, and predictive factors for response	BorDex	88
ThalDex	Palumbo 2001	Non-randomised, multicentre[a]	Efficacy and safety	ThalDex	77
	von Lilienfeld-Toal 2008	Systematic review of 12 phase II studies	Efficacy and safety	ThalDex	451
	Garderet 2012	Phase III, multicentre, open, randomised	Efficacy and safety	ThalDex BTD	269
BTD	Garderet 2012	See description under ThalDex combination			
BLD	Richardson 2009	Phase I, open-label, non-randomised	MTD (BorLen), efficacy, and safety	BorLen BLD	38

Study CC-5013 MM-009: Lenalidomide (Revlimid) Protocol CC-5013 MM-009: A multicenter, randomized, parallel-group, double-blind, placebo-controlled study of CC-5013 plus dexamethasone versus dexamethasone alone in previously treated subjects with multiple myeloma.

The applicant has provided a full clinical study report (dated 09 December 2008), with the consent of the sponsor (Celgene Europe Limited).

Subjects were enrolled from 11 Feb 2003 at 48 sites in U.S. and 4 in Canada. Inclusion criteria were prior or current diagnosis of Durie-Salmon stage II or III multiple myeloma and considered to have disease progression after at least 2 cycles of anti-myeloma treatment or to have relapsed with progressive disease after treatment; measurable levels of myeloma paraprotein (M-paraprotein) in serum (≥ 0.5 g/dL) or urine (≥ 0.2 g excreted in a 24-hour collection sample); and an ECOG performance status of 0, 1, or 2.

Eligible subjects were randomised in a 1:1 ratio to lenalidomide + oral dexamethasone (lendex) or dexamethasone alone (dex).

Subjects in the lendex group took 25 mg of lenalidomide orally once daily on Days 1 to 21 and a matching placebo capsule once daily on Days 22 to 28 of each 28-day cycle. Subjects in the dex group took 1 placebo capsule on Days 1 to 28 of each 28-day cycle. Subjects in both treatment groups took 40 mg of dexamethasone orally once daily on Days 1 to 4, 9 to 12, and 17 to 20 of each 28-day cycle for the first 4 cycles of therapy. Beginning with Cycle 5, the dose of dexamethasone was reduced to 40 mg orally once daily on Days 1 to 4 every 28 days for the remaining cycles.

The dexamethasone tablets for the combination therapy were obtained commercially by the subjects using prescriptions provided by the investigators.

The primary objective was to compare the efficacy of lendex with that of dex as treatment for subjects with relapsed or refractory multiple myeloma. Thesecondary objective was to compare the safety of lendex with that of dex as treatment for subjects with relapsed or refractory multiple myeloma.

Treatment continued until disease progression occurred or until treatment was discontinued for another reason. Adjustments of the lenalidomide and/or dexamethasone dose were made based on tolerability. The lowest allowable dose of oral dexamethasone was 20 mg daily for 4 days every 4 weeks.

The primary endpoint was time to progression (TTP) according to the Bladé criteria, with PFS and time to treatment failure as supportive analyses. Secondary endpoints included OS and myeloma response rate.

Randomisation was stratified according to prognostic features. The study was conducted as double-blind. The study was un-blinded after a pre-specified interim analysis demonstrated a treatment benefit in favour of the lendex combination. The study was ongoing (6 subjects in Canada) on the date of the study report. Data cut-off for primary analysis was 07 June 2005. Data cut-off for extended follow-up for survival was 23 Jul 2008.

The median age in the lendex and dex was 64.0 and 62.0 years respectively. A higher proportion of subjects in the lendex group (80.8%) than in the dex group (70.5%) had received prior therapy with dexamethasone (p = 0.026). 353 subjects were enrolled and analysed.

The median TTP was 60.1 weeks in the lendex group and 20.1 weeks in the dex group (p<0.001). At data cut-off for the interim analysis, 20.9% of patients in the lendex group had died compared to 34.1% in the dex, a statistically significant difference. Results of analysis of other secondary efficacy endpoints supported the primary efficacy outcome.

Study CC-5013 MM-010: Lenalidomide (Revlimid) Protocol CC-5013 MM-010: A multicentre, randomized, parallel-group, double-blind, placebo-controlled study of CC-5013 plus dexamethasone versus dexamethasone alone in previously treated subjects with multiple myeloma

The applicant has provided a full clinical study report (dated 09 December 2008), with the consent of the sponsor (Celgene Europe Limited). This protocol is virtually identical to MM-009 above, except that participants were from outside U.S.

Subjects were enrolled from 22 Sep 2003 at 55 sites in Australia, Europe and Israel. Inclusion criteria were prior or current diagnosis of Durie-Salmon stage II or III multiple myeloma and considered to have disease progression after at least 2 cycles of antimyeloma treatment or to have relapsed with progressive disease after treatment; measurable levels of myeloma paraprotein (M-paraprotein) in serum (≥ 0.5 g/dL) or urine (≥ 0.2 g excreted in a 24-hour collection sample); and an ECOG performance status of 0, 1, or 2.

Eligible subjects were randomised in a 1:1 ratio to lendex or dex alone. Subjects in the lendex group took 25 mg of lenalidomide orally once daily on Days 1 to 21 and a matching placebo capsule once daily on Days 22 to 28 of each 28-day cycle. Subjects in the dex group took 1 placebo capsule on Days 1 to 28 of each 28-day cycle. Subjects in both treatment groups took 40 mg of dexamethasone orally once daily on Days 1 to 4, 9 to 12, and 17 to 20 of each 28-day cycle for the first 4 cycles of therapy. Beginning with Cycle 5, the dose of dexamethasone was reduced to 40 mg orally once daily on Days 1 to 4 every 28 days for the remaining cycles.

Treatment continued until disease progression occurred or until treatment was discontinued for another reason. Adjustments were made in the lenalidomide and/or dexamethasone dose for each subject based on tolerability. The lowest allowable dose of oral dexamethasone was 20 mg daily for 4 days every 4 weeks.

The dexamethasone tablets for the combination therapy were obtained commercially by the subjects using prescriptions provided by the investigators.

The primary objective was to compare the efficacy of lendex with that of dex as treatment for subjects with relapsed or refractory multiple myeloma. The secondary objective was to compare the safety of lendex with that of dex as treatment for subjects with relapsed or refractory multiple myeloma.

The primary endpoint was time to progression (TTP) according to the Bladé criteria, with PFS and time to treatment failure as supportive analyses. Secondary endpoints included overall survival and myeloma response rate.

Randomisation was stratified according to prognostic features.

The study was conducted as double-blind. The study was un-blinded after a pre-specified interim analysis demonstrated a treatment benefit in favour of the lendex combination.

The study was ongoing on the date of the study report. Data cut-off for primary analysis was 03 August 2005. Data cut-off for extended follow-up for survival was 02 March 2008.

The median age in the lendex and dex groups was 63.0 and 64.0 years respectively. The treatment groups were comparable in demographic and disease-related characteristics and in prior anti-myeloma therapy at baseline.

351 subjects were enrolled and analysed, 176 in the lendex group and 175 in the dex group. The median TTP was 52.1 weeks in the lendex group and 20.1 weeks in the dex group ($p<0.001$). At data cut-off for the interim analysis, 27.3% of patients in the lendex group had died compared to 34.3% in the dex group. Results of analysis of other secondary efficacy endpoints supported the primary efficacy outcome.

Study CC-4047-MM-003: Pomalidomide (Imnovid) Protocol CC-4047-MM-003: A multicentre, randomized, parallel-group, open-label study of pomalidomide plus low dose dexamethasone versus high dose dexamethasone alone in subjects with refractory or relapsed and refractory multiple myeloma.

The applicant has provided a full clinical study report (dated 09 December 2013)

Subjects were enrolled from 18 March 2011 at 68 sites in Europe, 10 sites in Australia, 10 sites in Canada, 4 sites in Russia and one site in U.S. Eligible subjects had either refractory, or relapsed and refractory disease defined as documented disease progression during or within 60 days of completing their last multiple myeloma therapy. All subjects must have failed both lenalidomide and bortezomib. ECOG performance score had to be 0, 1 or 2.

Eligible subjects were randomised in a 2:1 ratio to pomalidomide + low dose oral dexamethasone (Pom + LD-dex) or high dose dexamethasone alone (HD-dex).

Subjects in the Pom + LD-dex group took 4 mg of pomalidomide orally once daily on Days 1 to 21 and dexamethasone 40 mg on days 1, 8, 15, and 22 of a 28-day cycle. Subjects in the HD-dex group took 40 mg of dexamethasone orally once daily on Days 1 to 4, 9 to 12, and 17 to 20 of each 28-day cycle. (Patients > 75 years of age in either treatment arm received dexamethasone 20 mg).

Treatment continued until disease progression. For subjects in the HD-dex arm whose disease progressed, the option was given to enrol in a companion study to receive pomalidomide alone.

The Sponsor provided commercial supplies of dexamethasone 2 mg and 4 mg tablets for oral administration.

The primary objective was to compare the efficacy of Pom + LD-dex with that of HD-Dex in subjects with refractory or relapsed and refractory multiple myeloma. The secondary objective was to compare the safety of Pom + LD-dex with that of HD-Dex in subjects with refractory or relapsed and refractory multiple myeloma.

The primary endpoint was PFS by blinded central review. The study was also powered to show an advantage in OS.

Randomisation was stratified according to prognostic features.

Data cut-off for primary analysis was 07 Sep 2012. Data cut-off for extended follow-up for survival was 01 Mar 2013. The majority of patients were male (58.9%) and white (78.5%). The median age was 64 years.

455 subjects were enrolled and analysed (ITT population), 302 in Pom + LD-dex arm and 153 in HD-Dex arm. The final PFS analysis was based on 267 events and was performed with a data cut-off of 07 Sep 2012. Median PFS was 15.7 weeks in the Pom + LD-dex arm compared to 8.0 weeks in the HD-Dex arm. The hazard ratio was 0.49 (95% CI: 0.39, 0.61). At 01 Mar 2013, the median OS was 54.0 weeks for the Pom + HD-dex arm, compared to 34.9 weeks for the HD-dex arm. The hazard ratio was 0.70 (95% CI: 0.54, 0.92).

Based on the PFS results and interim OS analysis, the DMC recommended study completion and cross-over of subjects from the HD-dex arm to the Pom + LD-dex arm.

Kobayashi 2010: Bortezomib plus dexamethasone for relapsed or treatment refractory multiple myeloma: the collaborative study at six institutes in Kyoto and Osaka

This is a retrospective observational cohort study investigating the efficacy and safety of patients with relapsed or refractory myeloma who had received bortezomib and dexamethasone (BD) therapy.

88 patients with relapsed/refractory multiple myeloma were treated with BD at 6 independent institutions in Kyoto and Osaka between 2003 and 2009. At least one cycle was administered to all 88 patients.

Bortezomib (1.3 mg/m^2/day) was intravenously administered on days 1, 4, 8 and 11, and dexamethasone (20 or 40 mg/day) was administered on days 1, 2, 4, 5, 8, 9, 11 and 12, with a 10-day rest period every 21 days. The dose of dexamethasone was reduced to 2–16 mg/day in 38 patients who previously experienced Grade 3 corticosteroid-related AEs, such as fluid retention, hyperglycemia, psychiatric disorders, or corticosteroid withdrawal symptoms.

Response was assessed using the International Myeloma Working Group (IMWG) criteria. PFS and OS were also measured. Factors in bortezomib and dexamethasone treatment suspected of having an effect on OS and PFS were analyzed by means of univariate analyses using log-rank tests.

Median age was 68 years. The median daily dose of Dexamethasone was 20 mg/day (range 2–40 mg/day). Overall ORR (CR + VGPR + PR) was 67.0%. The median OS was 510 days, and the estimated OS at 2 years was 41.4%, while the corresponding values for PFS were 113 days and 14.4%. Dexamethasone over 20 mg per day was associated with improved overall survival.

Palumbo 2001: Low-dose thalidomide plus dexamethasone is an effective salvage therapy for advanced myeloma

This was a prospective single arm study.

Between June 1999 and August 2000, 77 consecutive patients with refractory or relapsed myeloma were enrolled. At the time of treatment, all patients had progressive disease with a >50% increase in myeloma protein or reappearance of Bence Jones proteinuria >0.5 g/24h.

Thalidomide 100 mg daily was administered daily, in combination with dexamethasone on days 1 to 4 every month.

41% showed a myeloma protein decline >50%: in 18% the decline was 75-100%, in 23% it was 50-75%, and in 25% it was 25-50%. 3% showed complete remission.

Von Lilenfeld-Toal 2008: A systematic review of phase II trials of thalidomide/dexamethasone combination therapy in patients with relapsed or refractory multiple myeloma.

All trials published in the English language that evaluated combination therapy with thalidomide and dexamethasone in patients with relapsed or refractory multiple myeloma and had a clear definition of complete (CR) and partial remission (PR) were included. Trials were excluded if they reported only on patients with plasma cell leukaemia, solitary or extramedullary plasmocytoma.

12 studies, including a total of 451 patients, entered the final analysis. Most studies were single centre phase 2; there were no randomised controlled trials. Publication date was between 2000 and 2007. Median age was 63 years.

Dexamethasone regimens varied: 40 mg daily for days 1–4 every month in four studies (181 patients), 40 mg daily or 20 mg/ m^2 / day for days 1–4 every 3 weeks in three studies (66 patients), 12 mg daily days 1–4 every 3 weeks in one study (12 patients) and 20 mg/ m^2 days 1–5 every 15 days (47 patients). In two studies with 79 patients, the dexamethasone dose (40 mg daily days 1–4 or 20 mg/ m^2 / day) was repeated weekly or biweekly in the beginning of the treatment and then reduced to a monthly schedule. One study (n = 66) investigated 4 mg daily dexamethasone in the first month with a quick tapering of 1 mg/ day / week to a maintenance dose of 1 mg daily. There was no significant effect of dose intensity of dexamethasone on the response rate (P = 0.3).

Various criteria were used to evaluate response. The median remission rate (CR/PR) was 46% (95% CI 42-51%).

Garderet 2012: Superiority of the Triple Combination of Bortezomib-Thalidomide-Dexamethasone Over the Dual Combination of Thalidomide-Dexamethasone in Patients With Multiple Myeloma Progressing or Relapsing After Autologous Transplantation: The MMVAR/IFM 2005-04 Randomized Phase III Trial From the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation

Between 2006 and 2010, Patients with confirmed multiple myeloma and measurable disease were eligible if they had progressed or relapsed after at least one ASCT and provided it was their first progression or relapse. 269 patients were enrolled from 69 centres.

The study was open-label. Patients were randomly assigned 1:1 to receive bortezomib (1.3 mg/m^2 intravenous bolus) or no bortezomib for 1 year, in combination with thalidomide (200 mg per day orally) and dexamethasone (40 mg orally once a day on 4 days once every 3 weeks). Bortezomib was administered on days 1, 4, 8, and 11 with a 10-day rest period (day 12 to day 21) for eight cycles (6 months), and then on days 1, 8, 15, and 22 with a 20-day rest period (day 23 to day 42) for four cycles (6 months). Antithrombotic prophylaxis was mandatory in both arms. No crossover from the TD to the VTD arm was permitted.

This prospective phase III study compared the efficacy and safety of VTD versus TD in patients with multiple myeloma progressing or relapsing after ASCT.

The primary end point was TTP, defined as the interval from random assignment to disease progression, and was assessed on the intent-to-treat population. Secondary end points included PFS, OS, overall response rate (CR+PR), and safety. Progression and response were determined according to EBMT criteria.

Randomisation was stratified by number of previous ASCTs.

Baseline demographic data were well-balanced between treatment arms. Median age was 60 years and 62.6 years in the VTD and TD arms respectively.

No enrolled patients were excluded from the analysis.

Median time to progression was significantly longer with VTD than TD (19.5 vs 13.8 months; hazard ratio, 0.59; 95% CI, 0.44 to 0.80; p =0.001), the complete response plus near-complete response rate was higher (45% vs 25%; p=0.001), and the median duration of response was longer (17.2 vs 13.4 months; P=0.03).

The percentage of patients receiving planned doses of dexamethasone was 78.9% when randomly assigned to VTD therapy and 76.7% when randomly assigned to TD.

The most clinically significant AE was peripheral sensory neuropathy (grade 3), which occurred in 29% of patients on VTD and 12% on TD. Thromboembolic events were rare: five cases versus 10 cases of deep vein thrombosis and five cases versus two cases of pulmonary embolism for VTD versus TD.

Richardson 2009: Multicenter, phase I, dose-escalation trial of lenalidomide plus bortezomib for relapsed and relapsed/refractory multiple myeloma.

38 patients aged $\geq$ 18 years with relapsed or refractory multiple myeloma were enrolled across 6 dose cohorts. Median age was 59 years.

Patients received lenalidomide 5, 10, or 15 mg daily on days 1-14 and received bortezomib 1.0 or 1.3 mg/m^2 on days 1, 4, 8, and 11 of 21-day cycles. Dexamethasone (20mg or 40 mg on days 1, 2, 4, 5, 8, 9, 11, and 12 at the investigator's discretion) was added for progressive disease after two cycles. Dexamethasone dose could be reduced for attributable toxicity.

The primary objective was to evaluate safety and determine the MTD of lenalidomide + bortezomib in patients with relapsed/refractory multiple myeloma.

The MTD was lenalidomide 15 mg/ daily plus bortezomib 1.0 mg/m2. Among 36 response-evaluable patients, 61% (90% CI, 46% to 75%) achieved minimal response or better. Among 18 patients who had dexamethasone added (for progressive disease after two cycles), 83% (90% CI, 62% to 95%) achieved stable disease or better. 6 patients required dexamethasone dose reduction. To date, 13 of the 18 patients who received dexamethasone have subsequently experienced progression, and the median TTP was 6.1 months (95% CI, 2.7% to 14.6%) from the time of dexamethasone addition.

Supportive study

The applicant has submitted a patient questionnaire survey on high dose dexamethasone for subjects suffering from multiple myeloma (40 mg tablets).

The objective of the questionnaire was to evaluate the relevance of a new 40 mg dexamethasone tablet formation for high dose regimen for the treatment of patients suffering from multiple myeloma.

This was a cross-sectional survey using a postal questionnaire. The study participants were all members of a French patients organisation (Association Française des Maladies du Myélome Multiple). All 600 members of the organisation were sent a questionnaire with a covering letter. Questions covered tolerance (of current or most recent dexamethasone treatment), formulation and dose. Tolerance included questions regarding convenience, acceptability, preference and ease of dexamethasone regimen.

Of the 600 questionnaires sent, 282 responses were received, of which 260 were analysed (22 questionnaires did not contain any information regarding dexamethasone). The respondents were 136 male, 119 female. The median age was 65 years. 36% were taking dexamethasone currently. 49% and 17% of patients took one or half a tablet of dexamethasone per administration respectively. The remainder either took large numbers of tablets, or non-tablet formulations. 61% took 40 mg per administration; 33% took 20 mg per administration.

The highest acceptability score was associated with taking one tablet per administration (mean score 2.54 out of possible 3.0). The lowest score was associated with taking 80 tablets per administration (mean score 0.29). Around half of respondents answered a question regarding compliance changes associated with taking one tablet per administration, of which 44% thought compliance would improve, and 55% thought compliance would not change. However 78% of respondents would wish to receive one tablet per administration.

2.4.5. Clinical safety

Tabulated list of adverse reactions

The adverse reactions observed in patients treated with dexamethasone are listed below by system organ class and frequency.

Table 17. Adverse reactions observed in patients treated with dexamethasone

System organ class	Adverse reactions
Infections and Infestations	*Common*: Pneumonia, herpes zoster, upper respiratory tract infection, lower respiratory tract infection, oral candidiasis, oral fungal infection, urinary tract infection, herpes simplex, candidal infection; *Not known*: Infection, sepsis.
Blood and the lymphatic system disorders	*Common*: Neutropenia, anaemia, thrombocytopenia, lymphopenia, leukopenia, leukocytosis; *Uncommon*: Febrile neutropenia, pancytopenia, coagulopathy.
Endocrine disorders	*Common*: Cushing's syndrome; *Uncommon*: Hypothyroidism; *Not known*: Adrenal atrophy, steroid withdrawal syndrome, adrenal insufficiency, hirsutism, menstrual irregularity.
Metabolism and nutrition disorders	*Very common*: Hyperglycaemia; *Common*: Hypokalaemia, diabetes mellitus, anorexia, increased or decreased appetite, hypoalbuminaemia, fluid retention, hyperuricaemia; *Uncommon*: Dehydration, hypocalcaemia, hypomagnesemia; *Not known*: Glucose tolerance impaired, sodium retention, metabolic alkalosis.
Psychiatric disorders	*Very common*: Insomnia; *Common*: Depression, anxiety, aggression, confusional state, irritability, nervousness, mood alteration, agitation, euphoric mood; *Uncommon*: Mood swings, hallucinations; *Not known*: Mania, psychosis, behavioural disturbance.
Nervous system disorders	*Common*: Peripheral neuropathy, dizziness, psychomotor hyperactivity, disturbance in attention, memory impairment, tremor, paraesthesia, headache, ageusia, dysgeusia, somnolence, lethargy, balance impaired, dysphonia; *Uncommon:* Cerebrovascular accident, transient ischaemic attack, amnesia, coordination abnormal, ataxia, syncope; *Not known:* Convulsions.
Eye disorders	*Common*: Vision blurred, cataract; *Uncommon*: Conjunctivitis, increased lacrimation; *Not known:* Chorioretinopathy, glaucoma.
Ear and labyrinth disorders	*Common:* Vertigo.
Cardiac disorders	*Common:* Atrial fibrillation, supraventricular extrasystoles, tachycardia, palpitations; *Uncommon*: Myocardial ischaemia, bradycardia; *Not known*: Congestive heart failure.

Vascular disorders	*Common*: Venous thromboembolic reactions, predominantly deep vein thrombosis and pulmonary embolism, hypertension, hypotension, flushing, blood pressure increased, diastolic blood pressure decreased; *Not known:* Purpura, bruising.
Respiratory, thoracic, or mediastinal disorders	*Common*: Bronchitis, cough, dyspnoea, pharyngolaryngeal pain, hoarseness, hiccough.
Gastrointestinal disorders	*Very Common*: Constipation; *Common*: Vomiting, diarrhoea, nausea, dyspepsia, stomatitis, gastritis, abdominal pain, dry mouth, abdominal distension, flatulence; *Not known*: Pancreatitis, gastrointestinal perforation, gastrointestinal haemorrhage, gastrointestinal ulcer.
Hepatobiliary disorders	*Common:* Liver function tests abnormal, alanine aminotransferase increased.
Skin and subcutaneous tissue disorders	*Common*: Rash, erythema, hyperhidrosis, pruritus, dry skin, alopecia; *Uncommon*: Urticaria; *Not known:* Skin atrophy, acne.
Musculoskeletal and connective tissue disorders	*Very common*: Muscular weakness, muscle cramps; *Common*: Myopathy, musculoskeletal pain, arthralgia, pain in extremity; *Not known*: Pathological fracture, osteonecrosis, osteoporosis, tendon rupture.
Renal and urinary disorders	*Common*: Pollakiuria; *Uncommon:* Renal failure.
General disorders and administration site conditions	*Very common*: Fatigue, asthenia, oedema (including peripheral and facial oedema); *Common*: Pain, mucosal inflammation, pyrexia, chills, malaise; *Not known*: Impaired healing.
Investigations	*Common:* Weight decreased, weight increased.

Post marketing experience

Neofordex (dexamethasone) 40 mg scored tablet was granted a cohort Temporary Authorisation for Use (ATU) in France on 19 April 2010 in the following indications:

'Neofordex 40 mg is indicated as combination therapy for the treatment of certain forms of multiple myeloma, lymphoma and acute lymphoblastic leukaemia in adults.'

The applicant has provided post-marketing data. 12,141 patients with multiple myeloma have been exposed to Neofordex. Since the start of the ATU, 75 reports of adverse reactions have been collected. No amendments to section 4.8 of the SmPC are required in light of the reports received under the ATU.

2.4.6. Discussion on clinical aspects

The applicant has submitted data from study CPA 402-11, a single dose bioequivalence study in fasted healthy volunteers. The bioavailability of Neofordex 40 mg tablets is comparable to that of the reference product Dectancyl 0.5 mg tablets (Sanofi-Aventis France, France), as measured by AUC0-36. The Cmax of Neofordex 40 mg tablets is significantly lower than that of Dectancyl 0.5 mg tablets. The applicant has provided relevant non-clinical in vitro data to support the low relevance of the Cmax value in the clinical efficacy of dexamethasone in multiple myeloma treatment. The extrapolation of this non-clinical data to the clinical situation is considered acceptable. The pharmacokinetic study CC-5013-MM-017-PK provides some data relevant to the target population at the proposed daily dose level. AUCt and Cmax after a single dose (day 2) are in line with the values observed for the reference product in the bioequivalence study CPA 402-11 in healthy volunteers, when dose-adjusted. The half-life is also comparable.

The applicant has submitted clinical study reports from the literature, which include dexamethasone in various treatment combinations, or as a single-agent comparator, for previously untreated, or relapsed/refractory, multiple myeloma. Overall, the populations studied, which included a wide range of ages, as well as patients considered eligible or ineligible for ASCT, adequately reflect the proposed population of 'symptomatic multiple myeloma'. A wide range of combinations are investigated, including the newer immunomodulatory drugs and protease inhibitor, as well as more established cytotoxics. There is little evidence for the specific contribution of dexamethasone to efficacy, over and above some observed response outcomes in dexamethasone-only arms, or some suggestion of dose response. However, taken as a whole, the submitted literature provided evidence that dexamethasone, dosed at 20 mg or 40 mg daily, as pulse therapy, is an established therapy in the first line and relapsed / refractory settings.

Based on the literature data submitted, 40 mg once daily, administered as pulse therapy is widely used. However regimens using a 20 mg once daily dose are also recommended e.g. an attenuated regimen of cyclophosphamide, thalidomide and dexamethasone or CTDa (Ludwig et al 2012). The applicant has justified the advice to consider a dose of 20 mg daily in the elderly or frail patient based on expert consensus that 20 mg should be used in patients over 75 years (Dimopoulos 2011).

In addition, the applicant has conducted a questionnaire survey on high-dose oral dexamethasone (i.e., 40 mg daily doses, or 20 mg for elderly and/or frail patients) for subjects suffering from multiple myeloma in order to show the importance of a suitable dosage forms from a patient perspective.

In elderly and/or frail patients, the daily dose may be reduced to 20 mg of dexamethasone, according to the appropriate treatment regimen (SmPC, section 4.2).

Tablets may be broken in two equal halves using the score line to provide the 20 mg dose. Due to possible stability issues affecting half tablets stored after division, half-tablets that are not taken immediately should be discarded in agreement with local precautions for environmental protection (SmPC, section 4.2).

In order to eliminate the need to break the tablets if a 20 mg dose is prescribed, the Applicant commits to submit a marketing authorisation application (MAA) for 20 mg oral dosage form with an indication in MM.

A variation application to remove the score line should be submitted within 12 months of the first approval of a marketing authorisation for the 20 mg oral dosage form (see Risk Management Plan).

From the submitted data, 1958 patients with multiple myeloma, newly diagnosed or relapsed/refractory, were exposed to dexamethasone during clinical studies. The applicant has also submitted data from the Neofordex compassionate use programme set up in France: 12,141 patients with multiple myeloma received at least one dose of Neofordex.

The applicant has provided a description of the frequency of adverse events reported by multiple myeloma patients using mainly 40 mg daily as pulse therapy. This supplements the well-known safety profile of dexamethasone, for the purposes of the product information. In addition, the applicant has provided a summary of adverse reactions that have been observed more frequently and/or severely in treatment combinations including dexamethasone. The applicant's table of adverse reactions (ADRs) includes most of the ADRs listed for the reference product SmPC, and other EU marketed dexamethasone products. Additional ADRs are included, and frequencies of known ADRs upgraded, on the basis of the submitted safety data from dexamethasone only arms of submitted studies. This approach is endorsed and the updated frequencies are agreed. Some preferred terms have been grouped for the purposes of the SmPC. This is acceptable.

The applicant has highlighted serious adverse events which were reported in the submitted literature studies but which were not included in the reference product SmPC. The SmPC section 4.8 adequately describes the serious adverse events and deaths reported in the submitted literature. A specific warning regarding the risk of pneumonia has been included in Section 4.4 of the SmPC.

Haematological findings from the submitted literature data are adequately discussed by the applicant, and the SmPC updated accordingly.

The common adverse reactions to systemic corticosteroids may be associated with more serious consequences in old age, especially osteoporosis, hypertension, hypokalaemia, diabetes, susceptibility to infection and thinning of the skin. Close clinical supervision is required to avoid life-threatening reactions (SmPC, section 4.4).

No new data is submitted concerning the use of dexamethasone in pregnancy.

Based on human experience, dexamethasone is suggested to cause congenital malformations, particularly intra-uterine growth retardation and rarely neonatal adrenal insufficiency, when administered during pregnancy. Neofordex should not be used during pregnancy unless the clinical condition of the woman requires treatment with dexamethasone (SmPC section 4.6).

Glucocorticoids are excreted in human milk and effects have been shown in breastfed newborns/infants of treated women. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Neofordex therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman (SmPC, section 4.6).

Dexamethasone has been used for many years in Europe for a wide-range of indications, and its safety profile is well known. The submitted publications provide additional safety data at high dose, for the symptomatic multiple myeloma population, and in combination with other medicinal products.

2.4.7. Conclusions on clinical aspects

Pharmacokinetic comparability with the reference product has been demonstrated. A summary of the literature with regard to clinical data of dexamethasone was provided and was accepted by the CHMP. This is in accordance with the relevant guideline and additional clinical studies were not considered necessary.

2.5. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan (RMP):

The PRAC considered that the RMP version 3.4 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC advice dated 10 December 2015 via written procedure.

The CHMP endorsed this advice.

The applicant implemented the changes in the RMP as above requested.

The CHMP endorsed the RMP version 3.5 with the following content:

Safety concerns

Table 18. Summary of the Safety Concerns

Important identified risks	• Arterio-venous thromboembolism (predominantly deep vein thrombosis and pulmonary embolism) • Myelosuppression (predominantly thrombocytopenia and neutropenia) • Infections • Psychiatric disorders • Interaction with live attenuated vaccines • Interaction with high dose acetylsalicylic acid
Important potential risks	• Off-label use • Medication error related to administration of 20 mg dose • Interaction with oral contraceptives • Interaction with oral anticoagulants • Interaction with erythropoeitic medicinal products
Important missing information	• Use in patients with hepatic impairment • Use in sub-population carrying known and relevant genetic polymorphism, including CYP3A4, CYP2D6 and MRP1, MRP3 and MRP4.

Pharmacovigilance plan

The Applicant is required to address the following post-authorisation measures (PAMs).

Study / activity Type, title and category (1-3)	**Objectives**	**Safety concerns addressed**	**Status (planned, started)**	**Date for submission**
Development of a 20 mg oral dosage form to supplement Neofordex 40 mg Tablets. Category 3	To reduce the potential for medication errors with Neofordex 40 mg	Medication error related to administration of 20 mg dose	planned	A marketing authorisation application for a 20 mg oral dosage form should be filed within 12 months of the authorisation of Neofordex 40 mg Tablets.
Removal of the score line for sub-	To reduce the potential for	Medication error related to	planned	A variation application should

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission
division of the 40 mg tablet, and consequent deletion of the 20 mg posology Category 3	medication errors with Neofordex 40 mg	administration of 20 mg dose		be submitted within 12 months of the first approval of a marketing authorisation for the 20 mg oral dosage form

Risk minimisation measures

The PRAC considers that NO additional risk minimisation measures (RMMs) are necessary for the safe and effective use of the product.

Table 19: **Summary table of Risk Minimisation Measures**

Safety concern	***Routine risk minimisation measures***	***Additional risk minimisation measures***
Arterio-Venous Thromboembolism (predominantly deep vein thrombosis and pulmonary embolism)	*SmPC wording in Sections 4.4, 4.5, 4.8.*	*None*
Myelosuppression (predominantly thrombocytopenia and neutropenia)	*SmPC wording in Sections 4.4, 4.8.*	*None*
Infections	*SmPC wording in Section 4.4.*	*None*
Psychiatric disorders	*SmPC wording in Section 4.4.*	*None*
Interaction with live attenuated vaccines	*SmPC wording in Sections 4.4, 4.5.*	*None*
Interaction with high dose acetylsalicylic acid	*SmPC wording in Section 4.5.*	*None*
Off-label use	*Considering that the use of high-dose dexamethasone is already well-established in some other diseases (See Section SVI.5) risk minimization measures for off-label use are not required in addition to the routine pharmacovigilance. Additional measures may be taken in the future based on the collected pharmacovigilance data.*	*None*
Medication error related to administration of 20 mg dose	*Text is included in the patient information leaflet to advice patients to ask for help with breaking tablets as needed. Patients are also advised in the leaflet to discard unused half tablets that are not taken immediately, in order to avoid degradation. Complementary information is included in the SmPC, Sections 4.2, 6.4, 6.6.* *In printed matter of the SmPC and the Patient Leaflet, the paragraphs on handling of the 20 mg dose will be presented in boxed text to make it more prominent*	*None*

Safety concern	*Routine risk minimisation measures*	*Additional risk minimisation measures*
Interaction with oral contraceptives	*SmPC wording in Sections 4.5, 4.6.*	*None*
Interaction with oral anticoagulants	*SmPC wording in Section 4.5.*	*None*
Interaction with erythropoeitic medicinal products	*SmPC wording in Sections 4.4, 4.5, 4.8.*	*None*
Use in patients with hepatic impairment	*SmPC wording in Section 4.4.*	*None*
Use in sub-population carrying known and relevant genetic polymorphisms, including CYP3A4, CYP2D6, MRP1, MRP3 and MRP4 polymorphism	*SmPC wording in Section 4.5.*	*None*

PSUR submission

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

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

2.6. Product information

2.6.1. User consultation

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

3. Benefit-risk balance

This application concerns a hybrid version of dexamethasone 40 mg tablets. The reference product Dectancyl, is indicated in combination with various types of chemotherapy for the treatment of lymphoid malignancies.

Nonclinical studies have been provided for this application and considered sufficient. From a clinical perspective, this application contains new data on the pharmacokinetics of the active substance; the applicant's clinical overview on efficacy and safety clinical aspects based on information from published literature was considered sufficient.

The bioequivalence study forms the pivotal basis with a with cross-over design under fasting conditions. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. Choice of dose, sampling points, overall sampling times as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The bioavailability of Neofordex 40 mg tablets is comparable to that of the reference product Dectancyl 0.5 mg tablets (Sanofi-Aventis France, France), as measured by AUC0-36. The Cmax of Neofordex 40 mg tablets is significantly lower than that of Dectancyl 0.5 mg tablets. The applicant has provided relevant non-clinical in vitro data to support the low relevance of the Cmax value in the clinical efficacy of dexamethasone in multiple myeloma treatment. The extrapolation of this non-clinical data to the clinical situation is considered acceptable.

A positive benefit/risk ratio can therefore be concluded.

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

In order to eliminate the need to break the tablets if a 20 mg dose is prescribed, the Applicant commits to submit a marketing authorisation application (MAA) for 20 mg oral dosage form with an indication in MM.

A variation application to remove the tablet score line should be submitted within 12 months of the first approval of a marketing authorisation for the 20 mg oral dosage form (see Risk Management Plan).

4. Recommendation

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Neofordex is not similar to Revlimid, Thalidomide Celgene, Imnovid, Farydak and Kyprolis within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See Appendix 1.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority decision that the benefit-risk balance of Neofordex in the treatment of symptomatic multiple myeloma in combination with other medicinal products is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

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

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

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

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

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

- **Risk Management Plan (RMP)**

The 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**

N/A

- **Obligation to conduct post-authorisation measures**

N/A

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

Not applicable.

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APPENDIX 1

Divergent Position

Divergent position

The undersigned members of the CHMP did not agree with the CHMP's positive opinion recommending the 20 mg posology in elderly and/or frail patients.

The SmPC includes a 20 mg posology which requires halving a 40 mg tablet. The unused unpackaged tablet half requires to be discarded as there is no approved in-use stability period for this product. In order to protect the environment, unused tablet halves will need to be stored until they can be disposed of appropriately. This practice raises a number of issues. There is a risk that tablet halves will be taken subsequently, with a potential reduction in efficacy. In addition, unused tablet halves may not be stored out of the sight and reach of children.

The RMP includes medication error related to administration of the 20 mg dose as an important potential risk. Consequently, the applicant is requested to develop a 20 mg oral dosage form to supplement Neofordex 40 mg Tablets. Upon authorisation of the 20 mg strength oral dosage form, the applicant is requested to remove the score line for sub-division of the 40 mg tablet, and delete the 20 mg posology. These post-authorisation measures are classified as 'RMP'.

In order to fulfil the PAMs, the Applicant plans to gain approval for a dexamethasone 20 mg / 5 ml oral solution via the decentralised procedure. The oral solution will contain dexamethasone sodium phosphate, a different ester form to that of the Neofordex Tablet, which contains dexamethasone acetate. The applicant estimates that it could take up to 29 months for the 20 mg oral dosage form to be available in all relevant member states. It will then take a minimum of 6 months to remove the score line from the 40 mg tablet. Therefore it could be 3 years before the score line is removed and the 20 mg posology deleted.

The undersigned members of the CHMP believe that the risks associated with halving tablets, in the context of a formulation without in-use stability for the remaining tablet, and the approximate 3-year timeframe to remove the scoreline based on availability of a more suitable formulation outweigh the uncertain benefits of this formulation in terms of patient convenience. The 20 mg posology should be deleted prior to approval, and the score line should be removed prior to marketing.

London, 17 December 2015

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Greg Markey (United Kingdom)

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Robert James Hemmings (United Kingdom)

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Harald Enzmann (Germany)

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Jan Mueller-Berghaus (Germany)

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Daniel Brasseur (Belgium)

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Jean-Luis Robert (Luxembourg)

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Pieter de Graeff (The Netherlands)

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