



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Neofordex

International non-proprietary name: dexamethasone

Procedure No.: EMEA/H/C/002418/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted. On 17 July 2014, Laboratories CTRS officially notified the Committee for Medicinal Products for Human Use (CHMP) that it wishes to withdraw its application for a marketing authorisation for Neofordex, for the treatment of multiple myeloma.

For further information please refer to the Q&A which followed the company's withdrawal of the application: http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2014/07/WC500170185.pdf



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List of abbreviations

ACTH	Adrenocorticotrophic Hormone
AE	Adverse Event
allo-SCT	Allogeneic Stem Cell Transplantation
AP-1	Activator Protein 1
ASCT	Autologous Stem Cell Transplantation
AUC	Area Under the Curve
ATC	Anatomical Therapeutic Chemical
ATU	Autorisation Temporaire d'Utilisation
auto-SCT	Autologous Stem Cell Transplantation
Bor	Bortezomib
BLD	Bortezomib, Lenalidomide and Dexamethasone
BMI	Body Mass Index
BMSC	Bone marrow stromal cells
BTD	Bortezomib, Thalidomide, and Dexamethasone
BTD PACE	Bortezomib, Thalidomide, and Dexamethasone plus Cisplatin, Doxorubicin, Cyclophosphamide, and Etoposide
CHMP	Committee for Human Medicinal Products
CI	Confidence Interval
CL	Total Clearance
CL/F	Apparent Clearance
C _{max}	Average Maximum Concentration
CR	Complete Response
CRD	Cyclophosphamide, Lenalidomide, and Dexamethasone
CRF	Corticotrophin releasing factor
CRH	Corticotrophin releasing hormone
CTD	Cyclophosphamide, Thalidomide, and Dexamethasone
CTDa	Attenuated Cyclophosphamide, Thalidomide, and Dexamethasone
CVAD	Cyclophosphamide, Vincristine, Adriamycin and Dexamethasone
CVD	Cyclophosphamide, Bortezomib, and Dexamethasone
Cyc	Cyclophosphamide
CYP	Cytochrome
DCEP	Dexamethasone, Cyclophosphamide, Etoposide, and Cisplatin,
Dex	Dexamethasone
Dex Cons	Dexamethasone Dosing During Consolidation Therapy
Dex Ind	Dexamethasone Dosing During Induction Therapy
Dex Maint	Dexamethasone Dosing During Maintenance Therapy

DOR	Duration of Response
DST	Dexamethasone Suppression Test
DVT	Deep Vein Thrombosis
EBMT	European Group for Blood and Marrow Transplantation
ECOG	Eastern Cooperative Oncology Group
EFS	Event Free Survival
F	Female
GC	Gas chromatography
GCP	Good Clinical Practice
GD	Gestation days
GLP	Good Laboratory Practices
GR	Glucocorticoid receptor
HPLC	High performance liquid chromatography
HR	Hazard Ratio
ICH	International Conference on Harmonisation
IêBá	Inhibitor of $\kappa\text{B } \alpha$
IL-6	Interleukin-6
IMiD	Immunomodulatory Drug
IMWG	International Myeloma Working Group
INN	International Nonproprietary Name
ISS	International Staging System
ITP	Idiopathic Thrombocytopenic Purpura
IV	Intravenous
k_e	Elimination Rate Constant
Len	Lenalidomide
LenDex	Lenalidomide plus Dexamethasone
M	Male
MAA	Marketing Authorisation Application
MedDRA	Medical Dictionary for Regulatory Activities
MGUS	Monoclonal Gammopathy of Undetermined Clinical Significance
MM	Multiple Myeloma
MP	Melphalan plus Prednisone
MR	Minimal Response
MPR	Melphalan, Prednisone, and Lenalidomide
MPT	Melphalan, Prednisone, and Thalidomide
M-protein	Monoclonal Protein
MTD	Maximum Tolerated Dose
N	Total Number of Patients

NA	Not Applicable
NAV	Not Available
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
nCR	Near Complete Response
NF-κB	Nuclear Factor Kappa-light-chain-enhancer of activated B cells
NLT	Not less than
NMT	Not more than
NOAEL	No observed adverse effect level
NR3C1	Glucocorticoid Receptor Gene
ORR	Overall Response Rates
OS	Overall Survival
PACE	Cisplatin, Doxorubicin, Cyclophosphamide, and Etoposide Methasone.
PlaceboDex	Placebo plus Dexamethasone
PAD	Bortezomib, Doxorubicin and Dexamethasone
PegLD	Pegylated Liposomal Doxorubicin
PFS	Progression Free Survival
PMDD	Premature Drug Discontinuation
PN	Peripheral Neuropathy
PND	Postnatal day
PR	Partial Response
Pred	Prednisone
PTK- α	Protein-tyrosine kinase 2-beta
Rel/Ref	Relapsed/Refractory
PRS	Post-Relapse Survival
Rd	Rd, lenalidomide plus low-dose dexamethasone
RH	Relative humidity
RMP	Risk Management Plan
ROA	Route of Administration
R ²	Coefficient of Correlation
SCT	Stem Cell Transplant
SD	Stable Disease
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SWOG	Southwest Oncology Group
TAD	Thalidomide, Doxorubicin, and Dexamethasone
TCD	Thalidomide, Cyclophosphamide and Dexamethasone
TD	Thalidomide and Dexamethasone
Thal	Thalidomide

ThalDex	Thalidomide plus Dexamethasone
TK	Thymidine kinase
T _{max}	Time of Maximum Concentration
TNT	Time to Next Therapy
TRAIL	TNF-related apoptosis-inducing ligand
TT3	Total Therapy 3
TTP	Time to Progression
TTR	Time to Response
t _{1/2}	Terminal Half-Life
UV	Ultraviolet
VAD	Vincristine, Adriamycin/Doxorubicin and Dexamethasone
VCD	Bortezomib, Cyclophosphamide, and Dexamethasone
Vd _{ss}	Volume of distribution at steady state
VDT-PACE	Bortezomib, Dexamethasone, Thalidomide, Cisplatin, Doxorubicin, Cyclophosphamide, and Etoposide
VD	Volume of Distribution
VGPR	Very Good Partial Response
VMP	Bortezomib, Melphalan, and Prednisone
VRD	Bortezomib, Lenalidomide and Dexamethasone
VTD	Bortezomib, Thalidomide, and Dexamethasone

1. Recommendation

Based on the review of the data and the Applicant's response to the CHMP LoQ on quality, safety and efficacy, the CHMP considers that the application for Neofordex 40 mg Tablet, an orphan medicinal product, in the treatment of adults with symptomatic multiple myeloma in combination with other medicinal products, **is not approvable** since major quality objections still remain, which preclude a recommendation for marketing authorisation at the present time. These major objections are summarised as follows:

A number of quality major objections have been raised, casting doubt on control of the drug substance and the stability of the drug product.

Further substantial data require to be provided to assure the CHMP that the control strategy, test methods and stability of the drug substance and product are suitable to ensure reproducible product performance in line with the batch for which bioavailability data was presented.

Questions to be posed to additional experts

None

Inspection issues

None

New active substance status

Based on the review of the data the CHMP considers that the active substance dexamethasone contained in the medicinal product Neofordex 40 mg Tablets is not to be qualified as a new active substance in itself.

2. Executive summary

2.1. Problem statement

Neofordex 40 mg Tablet has been developed as a high strength tablet for use in combination with other agents in the treatment of symptomatic multiple myeloma. The tablets are scored and can be broken into halves to deliver 20 mg if required. The Applicant has provided bibliographic evidence to support the use of dexamethasone at a daily dose of 40 mg in this indication. Dexamethasone tablet formulations currently approved in member states range from 0.5 mg to 8.0 mg strength, according to the applicant. At the present time, no adequate high strength (40 mg or 20 mg) oral formulation of dexamethasone is available in Europe.

The therapies thalidomide, lenalidomide, pomalidomide and bortezomib are centrally authorised for the treatment of multiple myeloma with the following indications:

Thalidomide Celgene hard capsules (EU/1/08/443/001):

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

Revlimid (lenalidomide) hard capsules (EU/1/07/391/001-006):

Revlimid in combination with dexamethasone is indicated for the treatment of multiple myeloma in adult patients who have received at least one prior therapy.

(The posology for Revlimid recommends a dexamethasone regimen using 40 mg once daily).

Pomalidomide Celgene 1 mg hard capsules – [This medicinal product has been approved under the name Imnovid (EU/1/13/850/001-004)]

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

(The posology for Pomalidomide Celgene recommends a dexamethasone regimen using 40 mg once daily).

Velcade (bortezomib) powder for solution for injection (EU/1/04/274/001-002):

VELCADE as monotherapy is indicated for the treatment of adult patients with progressive multiple myeloma who have received at least 1 prior therapy and who have already undergone or are unsuitable for bone marrow transplantation.

VELCADE in combination with melphalan and prednisone is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for high-dose chemotherapy with bone marrow transplant.

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.

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 or vincristine + doxorubicin + high dose dexamethasone (VAD) have been used. In recent years, the introduction of the immunomodulatory drugs (thalidomide, lenalidomide, pomalidomide) and the proteasome inhibitor bortezomib have changed the management of myeloma and extended overall survival.

2.2. About the product

Neofordex 40 mg tablets is a high dose oral dexamethasone formulation. Dexamethasone (9 α -fluoro-16 α -methylprednisolone) combines high glucocorticoid activity with low mineralocorticoid activity.

Proposed indication:

Neofordex is indicated in adults for the treatment of symptomatic multiple myeloma in combination with other medicinal products.

Proposed posology:

Treatment must be initiated and monitored under the supervision of physicians experienced in the management of multiple myeloma.

Posology

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.

Elderly population

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

Patients with hepatic impairment or renal insufficiency

Patients with hepatic impairment or renal insufficiency require appropriate monitoring; patients with hepatic impairment should be dosed with caution as there are no data for this patient population (see sections 4.4 and 5.2).

Paediatric population

There is no relevant use of Neofordex in the paediatric population in the indication multiple myeloma.

Method of administration

Oral use.

In order to minimise insomnia, the tablet should preferentially be taken in the morning.

Tablets may be broken in two equal halves using the score line to provide the 20 mg dose.

2.3. The development programme/Compliance with CHMP guidance/Scientific advice

No CHMP scientific advice or protocol assistance has been sought in connection with the clinical development programme. The applicant has followed the CHMP *Guideline on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1).

2.4. General comments on compliance with GMP, GLP, GCP

A QP Declaration and Certificate of GMP Compliance (batch release site) has been presented. As a result, no inspections of the drug substance manufacturing site, the drug product manufacturing site or the batch release site are considered necessary.

Since a literature review has been presented, it cannot be verified whether the studies cited were conducted in compliance with the GLP regulations; however, it is assumed that the studies performed by the originator would have been conducted in compliance with the standards prevailing at the time.

According to a statement provided by the applicant, study CPA 402-11 has been performed in compliance with good clinical practice (GCP) including the archiving of essential documents. The applicant has not carried out any other clinical studies.

2.5. Type of application and other comments on the submitted dossier

This hybrid application is made in accordance with Article 6 of Regulation (EC) No 726/2004, as amended and Article 10(3) of Directive 2001/83/EC, as amended. The reference product is Dectancyl (dexamethasone acetate) 0.5 mg Tablets, by Sanofi-Aventis, approved in France since 31 Dec 1997 (MA number 34009 302 853 6 7). This is considered a suitable reference product. The applicant is seeking an indication 'in adults for the treatment of symptomatic multiple myeloma in combination with other medicinal products.' This differs from that of the reference product which describes a wide range of oncology and other conditions, but includes 'in combination with various types of chemotherapy for the treatment of lymphoid malignancies.' The strength of the proposed product also differs from that of the reference product.

3. Scientific overview and discussion

3.1. Quality aspects

Drug substance

The source of dexamethasone acetate is the subject of a current CEP. The specification proposed for the drug substance manufacturer is acceptable, however in light of its known polymorphism, low aqueous solubility and proposed use in a solid oral dosage form; additional controls have been requested from the drug product manufacturer.

The Applicant's studies and data from the drug substance supplier have now identified a number of polymorphic forms of the anhydrous drug substance. In the absence of *in vivo* data, polymorphic composition should be assumed to have potential to impact bioavailability. The absence of a test and control limit for polymorphic composition at release and retest has been elevated to a major concern.

Drug product

Neofordex 40 mg tablets are presented as uncoated, white, immediate release tablets with a scoreline to allow sub-division to yield a 20 mg unit dose when required. It is proposed that a 20 mg unit dose presentation is developed as a post-authorisation measure.

Formulation development is outlined with an emphasis upon manufacturability. A revised dissolution method has been proposed. The view of the CHMP is that demonstration of discrimination remains inadequate.

Manufacture is conventional, comprising dry blending of drug substance with excipients, followed by direct compression. Sufficient information has been presented regarding process development and controls. Excipient choice is typical for an immediate release tablet presentation; all are controlled to the relevant Ph. Eur. monographs.

The proposed specification is largely satisfactory; however justification of the proposed dissolution control limits requires further review and justification. The product is packed in a PVC/PVdC/Aluminium blister presentation.

Up to 36 months real-time (25oC/60%RH), 12 months intermediate (30oC/65%RH) data and 6 months accelerated (40oC/75%RH) stability data are presented for five lots of the proposed commercial drug product. Two lots are manufactured at commercial scale and representative of the proposed site of manufacture. These data are sufficient to demonstrate chemical stability; however dissolution data generated by the revised methodology had not been presented. Satisfactory photostability data have been presented in line with ICH guidance.

From a further stability study, limited dissolution data comprising up to 6 months data for a single batch have been presented. In stability studies, most test parameters including related substances and assay show no apparent significant change in line with earlier studies. However, dissolution data shows a marked drop with time and temperature, in both rate and extent of release. No mechanism for this change in dissolution performance is postulated. thus a change in the crystal form of the drug substance cannot be ruled out. In light of these changes, substantial further stability data in line with ICH guidance and equivalent to at least 6 months stability data for three batches are required to confirm the shelf-life and temperature storage condition.

Discussion on chemical, pharmaceutical and biological aspects

Dexamethasone acetate has a very low aqueous solubility (< 10 mcg/ml). As bioavailability may be dissolution-rate limited, a stringent control strategy is required to ensure the consistency of *in vivo* drug product performance.

Data for an *in vivo* comparison of bioavailability/bioequivalence for Neofordex 40 mg Tablet versus the Reference product, Dectancy 0.5 mg Tablets was investigated in study CPA 402-11, utilising a 20 mg total dose for each arm. Neofordex 40 mg tablets were sub-divided to provide the 20 mg dose.

The bioequivalence data do not comply with guideline CPMP/EWP/QWP/1401/98, with 90% confidence intervals around the test/reference mean ratio of the log normal pharmacokinetic variables for C_{max} outside the range of 80.00 to 125.00%. It is noted that C_{max} is approximately half and T_{max} approximately double that of the same dose of reference product.

Conclusions on the chemical, pharmaceutical and biological aspects

A number of quality major objections have been raised, particularly in light of significant new data, casting doubt on control of polymorphic composition of the drug substance and the stability of the drug product. The discrimination of revised dissolution method has not been unequivocally demonstrated, particularly with regard to variability in polymorphic composition and particle size distribution of the drug substance.

Further substantial data require to be provided to assure the Rapporteurs that the control strategy, test methods and stability of the drug substance and product are suitable to ensure reproducible product performance in line with the batch for which bioavailability data was presented.

3.2. Non clinical aspects

Pharmacology

A series of *in vitro* studies were conducted to investigate the effect of dexamethasone, thalidomide, its analogues (immunomodulatory derivatives or drugs [IMiDs] lenalidomide or pomalidomide) and proteasome inhibitors (bortezomib or carfilzomib) on myeloma cell death. Dexamethasone has been shown to induce multiple myeloma cell death via a down-regulation of Nuclear Factor- κ B (NF- κ B; a nuclear transcription factor that regulates the expression of a large number of genes involved in the regulation of apoptosis) activity and an activation of caspase-9 through second mitochondria-derived activator of caspase (Smac; an apoptosis promoting factor) release. IL-6 and high bcl-2 (an apoptosis regulator protein thought to be involved in chemoresistance) levels antagonised dexamethasone induced apoptosis. 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 I κ B- α protein levels. Thalidomide, IMiDs and proteasome inhibitors, also showed myeloma cell death-inducing activity and potentiated the apoptotic effect of dexamethasone.

An adequate summary of the major pharmacological actions of dexamethasone have been summarised comprising: (a) general effects on metabolism, water and electrolyte balance; (b) negative feedback effect on the hypothalamus and pituitary; (c) anti-inflammatory and immunosuppressive effects.

The Applicant states that safety pharmacology studies were not conducted with dexamethasone as it has been used in the clinic for many years and produced no effect on vital functions. Safety pharmacology studies were therefore not deemed necessary. This is acceptable. .

An adequate summary of the pharmacodynamic interactions of dexamethasone with thalidomide, its IMiDs, proteasome inhibitors and erythropoiesis-stimulating agents has been provided.

Pharmacokinetics

In rats orally administered 10 mg/kg [3H]-dexamethasone, the systemic exposure was 2.3×10^{-5} mol/L. In humans, the oral bioavailability of dexamethasone is 76%. Limited non-clinical data concerning the absorption of dexamethasone have been submitted.

In a clinical study, the bioequivalence (AUC) of the proposed Neofordex 40 mg tablet with the approved reference medicinal product Dectancyl 0.5 mg tablets was demonstrated.

In vitro, the binding of dexamethasone to plasma proteins in rat, dog, cow, and human was approximately 85, 73, 74, and 77%, respectively. Following intravenous administration in mice and rats, dexamethasone was detected mainly in the liver, gall bladder, bile, colon, kidney and muscle. A discussion of circumstantial evidence of the distribution of dexamethasone to the bone marrow was presented. In humans, dexamethasone displayed an apparent volume of distribution at steady state of 112 L.

Dexamethasone esters were shown to be rapidly hydrolysed in serum. *In vitro*, using liver microsomal preparations, dexamethasone was extensively metabolised to 6 hydroxydexamethasone and side-chain cleaved metabolites. Dexamethasone metabolism in rats and humans was comparable and principally involved hydroxylation to 6 hydroxydexamethasone. Dexamethasone was shown to be metabolised in the liver through hydroxylation via cytochrome P450 3A4 (CYP3A4), glucuronidation and sulphation. In rats, dexamethasone treatment increased liver and CYP3A4 mRNA and protein by 5 and 7-fold,

respectively, and increased intestinal and hepatic P-glycoprotein expression by 2 and 3 fold. This induction of CYP3A4 and P-gp is involved in many pharmacokinetic drug interactions.

Unchanged dexamethasone and its metabolites were excreted in the urine and bile.

An adequate summary of pharmacokinetic interactions of dexamethasone with other concomitantly administered medicinal products has been provided.

Toxicology

Single dose: The acute systemic toxicity of dexamethasone was low. In rats subcutaneously administered up to 120 mg/kg dexamethasone, mortality, body weight loss, growth arrest and abscesses in the lungs, kidneys, and/or liver were observed.

Repeated dose: In a number of oral, subcutaneous or intramuscular toxicity studies in rats and dogs administered dexamethasone, the effects observed included mortality, decreased body weight gain, organ weight, plasma and adrenal corticosteroid levels and increased levels of blood glucose, total 17 ketosteroid in urine, ALAT activity, serum lipid, adrenal triglycerides and adrenal and liver glycogen. Microscopical changes in the liver, adrenal and thymus tissues were also observed. NOAELs were not reported for any of the toxicity studies conducted. Most effects reversed following the cessation of dexamethasone treatment.

Toxicokinetics: Toxicokinetic analyses were not reported for any of the toxicology studies. This is acceptable as given the age of the original reports, toxicokinetic analyses would not have been expected. In addition, the clinical use of dexamethasone is well established.

Genotoxicity: Dexamethasone was not considered to be genotoxic in the *in vitro* and *in vivo* studies conducted.

Carcinogenicity: No carcinogenicity studies have been conducted with dexamethasone. This is acceptable. No carcinogenicity concerns have arisen during the many years of clinical use of dexamethasone.

Reproductive and developmental toxicity: A study in male mice, suggested that fertility may be decreased through germ cell apoptosis and spermatogenic defects. Data on female fertility are contradictory. While dexamethasone injection reduced ovarian hormonal production, ovulation, implantations and litter sizes in some experiments, in others it stimulated ovulation and increased litter size. In a study in pregnant rabbits, subcutaneous doses of dexamethasone reduced the number of embryonic implantation and live fetuses.

The teratogenic effects of dexamethasone (such as cleft palate and skeletal defects; decreased thymus, spleen and adrenal weight; lung, liver, and kidney abnormalities; and inhibition of growth) have been observed in a number of species. Post-natal development examination of animals treated prenatally with dexamethasone detected decreased glucose tolerance, insulin sensitivity, behavioural alterations and decreased brain and body weight.

In a juvenile toxicity study in rats administered dexamethasone on PND 7, body and brain weights were reduced and hyperactive behaviour was observed. There were also some indications of delayed development.

The effect of dexamethasone on reproductive development has been adequately summarised in the revised Non-clinical Overview. Sections 4.6 and 5.3 of the SmPC are generally considered adequate from a non-clinical perspective.

Local tolerance, antigenicity, immunotoxicity, dependence, metabolites: No local tolerance, antigenicity, immunotoxicity, dependence and metabolite studies with dexamethasone have been reported. This is acceptable as no concerns have arisen during the many years of clinical use that warrant the necessity for these studies.

Impurities: All impurities identified are below the identification/qualification threshold and present no toxicological concern.

Phototoxicity: No phototoxicity study with dexamethasone was reported. This is acceptable. Phototoxicity studies with dexamethasone are not considered necessary as no concerns have arisen during the many years of its clinical use.

Ecotoxicity/environmental risk assessment

No relevant environmental concerns are apparent from the use of dexamethasone provided the usual recommendations for disposal of unused drug are followed.

Discussion on non-clinical aspects

The dossier is compiled of published literature. In its response to the Day 120 LoQ, the Applicant has submitted data from a new non-clinical study 'Kinetics of dexamethasone activity in multiple myeloma cell lines.' This investigation was undertaken to test the hypothesis that, at constant exposure to dexamethasone, its pro-apoptotic activity is dependent on the duration of exposure and not the maximal concentration. Melphalan, an alkylating agent also used in multiple myeloma, was used as a comparator. While the design and description of this *in vitro* study is satisfactory from a non-clinical perspective, the results and their potential extrapolation to the clinic are discussed in detail within the Clinical (Pharmacodynamics) section of this overview.

The pharmacology, pharmacokinetics and toxicology studies summarised in the submitted dossier are adequate. In addition, the environmental risk assessment provided is acceptable.

Conclusion on non-clinical aspects

Overall the Non-clinical Overview could be considered broadly acceptable to support the clinical use of dexamethasone for the treatment of symptomatic multiple myeloma in combination with other agents.

3.3. Clinical aspects

Pharmacokinetics

Common excipients are used in the tablet formulation of Neofordex 40 mg tablet. None of the excipients, in the amounts used, is expected to have a significant impact on oral drug relative bioavailability.

The dissolution tests performed and submitted are in compliance with the guidance provided in the "Guideline on the Investigation of Bioequivalence" (CPMP/EWP/QWP/1401/98 Rev. 1).

To support the application, the applicant has submitted one relative bioavailability study CPA 402-11. The applicant has also provided an overview of the pharmacokinetics of dexamethasone, based on the literature, in order to support relevant sections of the SmPC.

The proposed posology is one 40 mg strength tablet daily, on specified days of a 28 day treatment cycle. However the SmPC (section 4.2) advises that in elderly and/or frail patients, the daily dose may be reduced to 20 mg, according to the appropriate treatment regimen. Tablets may be broken in two using the score to provide the 20 mg dose.

Only the 20mg dose has been investigated in healthy volunteers, on safety grounds. 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. The biowaiver justification is acceptable.

Study CPA 402-11 (EudraCT No.: 2011-006095-39)

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

Study design

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 Neofordex 40 mg tablets (44.3 mg of dexamethasone acetate equivalent to 40 mg of dexamethasone base) was administered as half a tablet, broken by hand, to provide a 20 mg molar dose. The reference product Dectancyl 0.5 mg tablets (0.5 mg of dexamethasone acetate equivalent to 0.451 mg of dexamethasone base) was administered as 44 tablets, to provide a 20 mg molar dose.

Dexamethasone has low solubility and the division of the reference product administered dose into 44 tablet units probably also has some impact on its in vivo dissolution when compared with a single tablet unit administration. The need to divide one Neofordex 40 mg tablet into two halves in order to obtain the 20 mg test product administered dose also introduces some variability within the test treatment since the real dexamethasone content of each half tablet is unknown as well as its variability. Furthermore, although the test and reference tablets were swallowed whole and were not chewed or broken, additional water (in volumes of 100 mL) was provided in some subjects to facilitate swallowing of such a high number of the reference tablets. However, following adequate discussion by the Applicant, none of these sources of variability are judged to be significant.

Blood samples were collected at 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. 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.

Twenty-four healthy volunteers completed the study and were included in the pharmacokinetic (PK) and statistical analysis. The primary PK parameters were AUC₀₋₃₆ and C_{max}. T_{max}, AUC_{0-∞}, residual area, λ_z, and half-life were also calculated. The 90% bioequivalence criteria were pre-defined as 80.00-125.00% for both AUC₀₋₃₆ and C_{max}.

Results

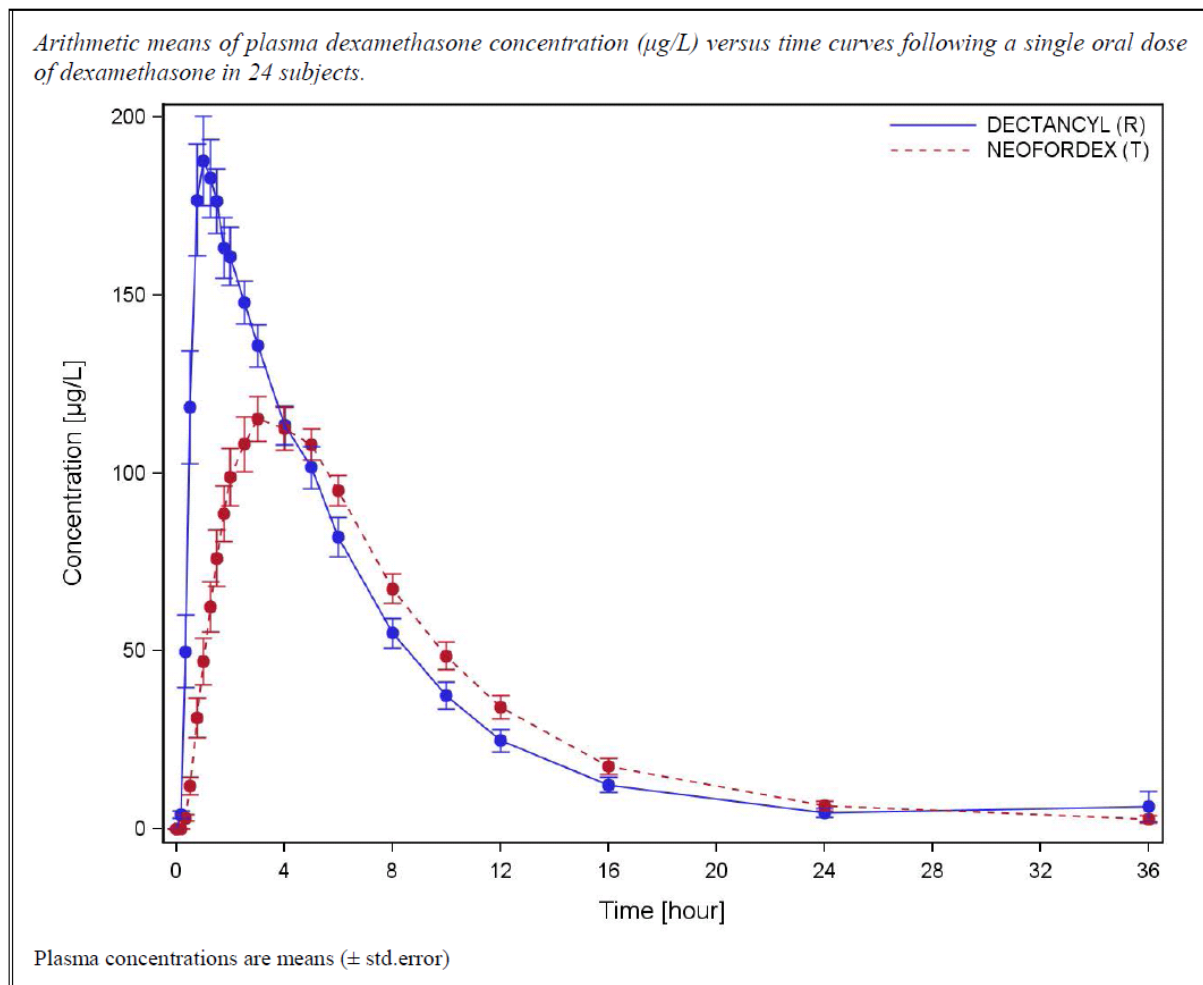
Table 1: Pharmacokinetic parameters for dexamethasone (non-transformed values)

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-∞) [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-∞}	area under the plasma concentration-time curve from time zero to infinity			
C _{max}	maximum plasma concentration			
T _{max}	time for maximum concentration (* median, range)			

Table 2: 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-∞)	94.47	89.26 - 99.99
C _{max}	59.75	56.32 - 63.38

Figure 1: Arithmetic means of plasma dexamethasone concentration versus time curves



Regarding AUC₀₋₃₆, the 90% CIs for the ln-transformed ratio of the geometric mean was 89.08 - 99.56%. This is well within the pre-specified bioequivalence criteria. Regarding C_{max}, the 90% CI for the ln-transformed ratio of the geometric mean was 56.32-63.38%. The test values were lower than the reference values in all subjects. T_{max} is significantly longer for the test product compared to the reference product.

The Applicant has provided an analysis of available PK data from study CC-5013-MM-017-PK (using a 4 mg dexamethasone formulation) and from the literature. Actual PK parameters observed for the test and reference product in study CPA-402-11 are compared to predicted PK parameters of dexamethasone, normalised to a 20 mg dose, as shown in Table 3:

Table 3: Experimental and Predicted Neofordex and DectancyI C_{max} and AUC_{0-t}

Parameter	Linear Regression	R ²	20 mg predicted	observed	% of	observed	% of
				20 mg Neofordex (test)	predicted	20 mg DectancyI (reference)	predicted
AUC ₀₋₂₄	y = 50.309x	0.9867	1006.18	1192	118.5	1117	111.0
C _{max}	y = 10.52x	0.9962	210.4	125.9	59.8	213.6	101.5

AUC units: µg • h/l, C_{max} units: µg/l

The Applicant has provided relevant non-clinical in vitro data to support the low relevance of the C_{max} value in the clinical efficacy of dexamethasone in multiple myeloma treatment. The Applicant has also provided a discussion of the relevance of the in vitro mechanism of action for the in vivo situation, based on data from the literature. Given the obvious limitations to conduct a conventional comparative clinical trial in patients (lack of an adequate reference formulation, presence of a number of confounding factors, number of patients to include) the extrapolation of this non-clinical data to the clinical situation is considered acceptable.

No safety concerns are raised following assessment of the safety data from this study.

Dexamathasone pharmacokinetics

The applicant has provided an overview of the pharmacokinetics of dexamethasone based on the SmPC of the reference product, supplemented by bibliographic data.

Absorption

The oral bioavailability of dexamethasone has been reported as 76%.

Distribution

Dexamethasone is bound to 77.4 ± 1.1% by plasma proteins; it has no affinity for transcortin and binds only to albumin.

Elimination

Terminal half-life is around 4 hours. Dexamethasone is metabolised in the liver, mainly by CYP3A4. At high doses (16-24 mg), dexamethasone also induces CYP3A4. Unchanged dexamethasone (< 10%) and metabolites are excreted in the urine. The applicant has provided detail in section 5.2 of the SmPC regarding the role of CYP3A4.

Dose and time proportionality

From an analysis of available PK data from the literature, the applicant has demonstrated linearity for dexamethasone within the dose range 0.5 mg to 300 mg.

Time dependent clearance and elimination half-life for dexamethasone was observed in patients with multiple myeloma treated with 40 mg (4 X10 mg) multiple doses of dexamethasone in study CC-5013-MM-017-PK [36% increase in the drug clearance and 24% decrease in AUC_τ without significant effect on the drug absorption rate (C_{max} and T_{max})]. The changes in dexamethasone CL/F and AUC₀₋₂₄ were considered to be due to auto induction of CYP3A4, the primary enzyme responsible for

dexamethasone metabolism. CYP3A4 induction may be additionally affected by the altered PK characteristics of the Neofordex formulation, particularly a longer Tmax. The potential for auto-induction is adequately described in Section 4.5 of the SmPC.

Special populations

Renal failure has been associated with an increased dexamethasone clearance of 65%, and resulting reduction in half-life of 30%. It is agreed that no dose adjustments are required in patients with renal impairment based on the literature data submitted.

Clearance is reduced by around 35%, and half-life increased, in patients with liver disease. Dexamethasone is mainly hepatically excreted. Therefore an increase in exposure would be expected for patients with hepatic impairment. A warning to monitor appropriately is included in section 4.4 of the SmPC. An appropriate warning is also included in section 4.2 for this special population, with cross-reference to sections 4.4 and 5.2.

Interactions

Dexamethasone is known to be a substrate and weak to moderate inducer of CYP 3A4. The Applicant has provided an adequate summary of the published literature on the pharmacokinetic drug interaction studies conducted with dexamethasone. Section 4.5 and section 5.2 of the SmPC have been updated to include information regarding CYP3A4 and P-gp induction.

In view of the proposed indication for use in the treatment of multiple myeloma in combination with other agents, the applicant has provided a discussion of the likelihood of clinically relevant pharmacokinetic interactions, for each drug combination foreseen, with reference to the available literature. It is agreed that dexamethasone has no clinically significant pharmacokinetic interaction with thalidomide, lenalidomide, bortezomib, vincristine or doxorubicin.

Pharmacodynamics

The applicant has provided a detailed discussion of the mechanism of action of dexamethasone in the treatment of multiple myeloma, based on available literature. In vitro data demonstrate that dexamethasone has a specific, apoptosis-inducing activity on myeloma cells. This activity is enhanced by the combination with immunomodulatory drugs (e.g. thalidomide and lenalidomide) and with protease inhibitors (e.g. bortezomib). Dexamethasone is thought to enter the cell by passive diffusion through the membrane and bind to a complex of gonadotrophin receptor and heat shock protein (Hsp) 90, releasing Hsp 90 and exposing the DNA-binding part of the receptor, which then migrates into the nucleus and binds to specific gene regulatory sequences in order to activate transcription. Apoptosis follows via a down-regulation of NF-κB activity and an activation of caspase-9 via Smac. Early apoptotic markers are detectable rapidly upon exposure to dexamethasone, but prolonged exposure is required to achieve peak levels of these markers, major caspase-3 activation and DNA fragmentation. The kinetics of dexamethasone-induced gene expression has also been investigated in vitro: the activity of various apoptosis-related genes peak at 24 hours. The applicant concludes that the anti-myeloma activity of dexamethasone is hence based on specific induction of apoptosis, relying on the activation of intricate cellular processes and requiring prolonged exposure.

New non-clinical data

The Applicant has submitted data from a new non-clinical study: 'Kinetics of dexamethasone activity in multiple myeloma cell lines.' The investigation was undertaken to test the hypothesis that, at constant exposure to dexamethasone, its pro-apoptotic activity is dependent on the duration of exposure and

not the maximal concentration. Melphalan, an alkylating agent also used in multiple myeloma, was used as a comparator.

Three human myeloma cell lines were used. The concentrations of dexamethasone and melphalan were chosen based on human in vivo pharmacokinetic data. The doses and durations of exposure to both agents were adequately justified and reflected the in vivo conditions.

Cell lines showing differing sensitivity to dexamethasone were chosen: OPM2, BCN and NAN8. The chromosomal translocations were also taken into consideration in the choice of cell lines, which were representative of two myeloma subgroups. The culture conditions and experimental procedures are adequately described. Three replicates were exposed for set culture periods and each experiment was conducted three times. Myeloma cell lines were exposed to different concentrations of dexamethasone for different times (6, 16, 24 or 40 hours) and to different concentrations of melphalan for 6 hours.

The results show that, at constant exposure to dexamethasone, cell survival decreased with increasing time, although the concentration of dexamethasone was lower in the cultures exposed for longer periods (to mimic the in vivo conditions). At 40 hours of exposure to dexamethasone, cell survival was significantly lower than at 6 hours in all three cell lines ($p < 0.05$). Cell survival in the BCN line was also significantly decreased at 24 hours ($p < 0.05$). After 6 hours exposure to a high concentration of dexamethasone, cell survival was affected only negligibly, in contrast to cells exposed to melphalan, in which exposure for 6 hours resulted in a concentration-dependent decrease in cell survival.

Apoptosis was measured in three experiments conducted in duplicate. Cell death was induced by dexamethasone only when it was in the medium, in contrast to melphalan, which induced irreversible cell death. The results showed that for dexamethasone, the induction of apoptosis was also dependent on the duration of exposure and not on the concentration. For all time points and all but one exposures, the increase in apoptosis was statistically significant ($p \leq 0.0001$).

The data from the cell survival and apoptosis measurements support the author's conclusion that for a given, clinically-relevant AUC (plasma concentration X time) of dexamethasone, the duration of exposure is the determining factor in decreasing cell survival and in increasing apoptosis. In contrast, melphalan induced apoptosis and reduced cell survival after a duration of exposure at which dexamethasone showed no effect. Over this short duration of exposure, the effects of melphalan were concentration dependent. The experiments appear to be adequately designed. The report is clear and the data are adequately presented and discussed.

The Applicant has provided relevant non-clinical in vitro data to support the low relevance of the C_{max} value in the clinical efficacy of dexamethasone in multiple myeloma treatment. The Applicant has also provided a discussion of the relevance of the in vitro mechanism of action for the in vivo situation, based on data from the literature. Given the obvious limitations to conduct a conventional comparative clinical trial in patients (lack of an adequate reference formulation, presence of a number of confounding factors, number of patients to include) the extrapolation of this non-clinical data to the clinical situation is considered acceptable.

Clinical efficacy

The proposed indication is "Neofordex is indicated in adults for the treatment of symptomatic multiple myeloma in combination with other medicinal products".

The proposed posology is:

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.

Elderly population

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

The applicant has submitted reports of clinical studies with dexamethasone formulations other than Neofordex 40 mg Tablets, to support the efficacy of dexamethasone in the treatment of symptomatic multiple myeloma, in combination with other agents. No clinical efficacy and safety studies have been conducted using Neofordex. Tables 4 and 5 summarise the submitted data, for first line and relapsed/refractory populations respectively:

Table 4: Overview of studies for first line treatment of multiple myeloma

Table 2.5-6: Overview of Studies for First Line Treatment of Multiple Myeloma

Drug 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.

Table 5: Overview of studies for treatment of relapsed/refractory multiple myeloma

Table 2.5-8: Overview of Studies for Treatment of Relapsed/Refractory Multiple Myeloma

Drug 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
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

Source: (Palumbo et al. 2001; von Lilienfeld-Toal et al. 2008; Richardson et al. 2009; Kobayashi et al. 2010; Garderet et al. 2012); CC-5013 MM-009 CSR synopsis, CC-5013 MM-010 CSR synopsis.

^a The phase of this clinical trial was not specified.

Bor: bortezomib, BorDex: bortezomib plus dexamethasone, BorLen: bortezomib plus lenalidomide, BLD: bortezomib, lenalidomide, and dexamethasone, Dex: dexamethasone, Len: lenalidomide, LenDex: lenalidomide plus dexamethasone, MTD: maximum tolerated dose, N: total number of patients, PlaceboDex: placebo plus dexamethasone, Thal: thalidomide, ThalDex: thalidomide plus dexamethasone.

Discussion on clinical efficacy

Data from clinical trials

High dose glucocorticoids have been used in the treatment of symptomatic multiple myeloma for over 50 years. Therefore it would be very difficult to design a clinical study to conclusively demonstrate the efficacy of dexamethasone in this clinical setting, either as single therapy or in combination. Instead, the applicant has submitted three clinical study reports (with permission from the relevant sponsor), and 12 studies 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 provides evidence that dexamethasone, dosed mainly at 40 mg daily, as pulse therapy, is an established therapy in the first line and relapsed/refractory settings.

Clinical guidelines

Several European treatment guidelines recommend dexamethasone in combination with other agents for the treatment of symptomatic multiple myeloma:

European Perspective on Multiple Myeloma Treatment Strategies: Update Following Recent Congresses (Ludwig et al 2012) makes recommendations for first line treatment which include dexamethasone in combination for induction prior to ASCT, and in patients not considered candidates for ASCT.

Dexamethasone is also an option in combination for consolidation, but no longer as maintenance. At first relapse, dexamethasone is an option in combination with other agents in both 2-drug and 3-drug regimens, in patients being considered for, or ineligible for, second ASCT.

Multiple myeloma: ESMO Clinical Recommendations for diagnosis, treatment and follow-up (Harousseau & Dreyling 2009) specifically recommends a dexamethasone-based induction therapy in patients age < 65 years prior to ASCT. In the relapsed/refractory setting, thalidomide or lenalidomide, in combination with dexamethasone, or bortezomib alone, or in combination with dexamethasone or cytotoxics, are recommended.

Proposed posology

There is little available data to guide dose-finding. Based on the literature data submitted, 40 mg daily, administered as pulse therapy e.g. days 1-4, 9-12, 17-20 of a 28 day cycle, or once weekly, is widely regarded as a standard dose. In several protocols, dose could be reduced to 20 mg daily if toxicities developed, but a starting dose of 20 mg daily was less common. However regimens using a 20 mg dose have been recommended e.g. 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).

The posology wording is acceptable.

The rationale for the development of only a 40 mg tablet is questioned, as according to the proposed posology, some patients may require a 20 mg daily dose (elderly and frail). In addition, some regimens include a 20 mg dose irrespective of age. A 20 mg presentation would avoid the need to subdivide the tablet, which could present difficulties for the elderly or frail patient. A post-authorisation measure to develop a 20 mg strength tablet is proposed.

Regulatory considerations

The reference product for this Article 10(3) hybrid application, Dectancyl 0.5 mg tablet, is approved, among other indications, in combination with various types of chemotherapy for the treatment of lymphoid malignancies. A UK marketed dexamethasone formulation also lists 'myeloma' as an indication (Dexsol 2mg/5ml Oral Solution PL 00427/0137). Revlimid (lenalidomide) hard capsules, a centrally authorised product, is indicated for: 'Revlimid in combination with dexamethasone is indicated for the treatment of multiple myeloma in adult patients who have received at least one prior therapy.' Imnovid 1 mg hard capsules are now centrally authorised: 'in combination with dexamethasone is indicated in the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy.'

Bioequivalence

In order to conclude a positive benefit-risk for this application, there needs to be adequate evidence that the efficacy of this dexamethasone formulation is comparable to that of the reference product, and currently marketed formulations. Since bioequivalence with an appropriate reference product has not been demonstrated, due to a low C_{max}, the Applicant was asked to provide a justification that a lower C_{max} would not result in reduced efficacy compared to currently marketed dexamethasone formulations.

In response to this question, the Applicant did not perform a comparative clinical efficacy study and the CHMP agrees it does not seem feasible to perform such a study in patients with multiple myeloma. The Applicant has provided relevant non-clinical *in vitro* data to support the low relevance of the C_{max} value in the clinical efficacy of dexamethasone in multiple myeloma treatment. The Applicant has also provided a discussion of the relevance of the *in vitro* mechanism of action for the *in vivo* situation, based on data from the literature. Given the obvious limitations to conduct a conventional comparative clinical trial in patients (lack of an adequate reference formulation, presence of a number of confounding factors, number of patients to include) the extrapolation of this non-clinical data to the clinical situation is considered acceptable.

Conclusions on clinical efficacy

The efficacy of dexamethasone in the treatment of symptomatic multiple myeloma, in combination with other medicinal products, is accepted, based on the bibliographic evidence submitted. In addition, the total exposure of Neofordex 40 mg tablets, as measured by AUC_{0-t}, is comparable to that of a European reference product. The C_{max} is low compared to the reference product, and also that predicted based on an analysis of available data for other formulations. The Applicant has provided new non-clinical *in vitro* data, and a literature-based discussion, to support the low relevance of the C_{max} value in the clinical efficacy of dexamethasone in multiple myeloma treatment. Given the obvious limitations to conduct a conventional comparative clinical trial in patients, the extrapolation of this non-clinical data to the clinical situation is considered acceptable.

Clinical safety

Dexamethasone has been used for many years in Europe for a wide-range of indications, and its safety profile is well known. The submitted case study reports and publications provide additional safety data at high dose, for the symptomatic multiple myeloma population, and in combination with other agents. The applicant has provided a discussion of the submitted data, with the aim of updating the known safety profile, as reflected in the product information of the reference product Dectancyl 0.5 mg, tablet, to be relevant for the proposed indication and posology.

Patient exposure

From the submitted data, 814 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: 6282 patients with multiple myeloma received at least one dose of Neofordex.

Adverse events

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. Data from dexamethasone only or dexamethasone/placebo treatment arms is used to supplement the table of ADRs in section 4.8 of the SmPC. 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, for inclusion in section 4.8 of the SmPC.

Serious adverse events and deaths

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. These are included in section 4.8 of the proposed SmPC. Haematological toxicities, thromboembolic disease and peripheral neuropathy are discussed in section 4.3 under 'combination treatment'. Other events reported as grade 3/4 toxicities, deaths or serious adverse events include pneumonia NOS, cardiac events (including myocardial infarction), intestinal perforation, cerebral oedema, pulmonary oedema, cerebrovascular accident and sepsis. Of these, the most common was pneumonia NOS. A specific warning regarding the risk of pneumonia is included in Section 4.4 of the SmPC.

Laboratory findings

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

Safety in special populations

Pregnancy and breast-feeding

No new data is submitted concerning the use of dexamethasone in pregnancy. Due to its known toxicity profile, dexamethasone should not be used in pregnancy at the proposed dose. In addition, it is likely to be used in combination with immunomodulatory drugs which are contraindicated in pregnancy, or other agents which are not recommended in pregnancy. Appropriate warnings are included in Section 4.6 of the SmPC. Additional warnings regarding the risk in combination with immunomodulatory drugs which are known teratogens have been included in Section 4.4.

The elderly

The median age of patients included in the submitted literature studies was lower than that seen in clinical practice. No specific data concerning adverse events in older multiple myeloma patients is presented. The SmPC section 4.2 advises:

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

[....]

Tablets may be broken in two using the score to provide the 20 mg dose.

The wording regarding this special population in Section 4.2 is considered acceptable. Given the high dose of dexamethasone, the elderly are likely to be particularly at risk of the known toxicities of dexamethasone treatment, particularly osteoporosis, hypertension, hypokalaemia, diabetes, infections, thinning of skin. Additional is included in Section 4.4 of the SmPC.

Hepatic and renal impairment

See under 'Pharmacokinetics'.

Immunological events

According to the SmPC of Dexasol 2mg/5ml Oral Solution, a UK marketed dexamethasone product approved for multiple myeloma, : 'hypersensitivity including anaphylaxis has been reported'.

Safety related to drug-drug interactions and other interactions

See under 'Pharmacokinetics'.

Discontinuation due to AES

Based on the submitted data, no SmPC changes are required, regarding discontinuation due to AEs.

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. 6282 patients with multiple myeloma have been exposed to Neofordex. Since the start of the ATU, 38 reports of adverse reactions have been collected. As requested, the Applicant has provided a detailed description and analysis of the 4 adverse reports received under the SOC 'skin and subcutaneous tissue disorder' from the latest periodic report of Neofordex, which has a 'temporary authorisation for use' in France. From the information provided, a causal relationship is unlikely for at least 2 of the reports. It is agreed that there is no signal for an increased risk of skin and subcutaneous tissue disorder. The information provided in Section 4.8 of the SmPC is considered adequate.

Discussion on clinical safety

The applicant has provided a discussion of the submitted data, with the aim of updating the known safety profile of dexamethasone, as reflected in the product information of the reference product Dectancy 0.5 mg, tablet, to be relevant for the proposed indication and posology. No major new safety issues have been raised during assessment of the submitted data from clinical study reports and the literature.

Conclusions on clinical safety

The safety profile of dexamethasone is well established, and remains acceptable for the proposed indication and posology following assessment of the submitted data.

Pharmacovigilance system

Reference should be made to the PRAC assessment report.

Risk management plan

Reference should be made to the PRAC assessment report.

3.4. New active substance status

Based on the review of the data the CHMP considers that the active substance dexamethasone contained in the medicinal product Neofordex 40 mg Tablets is not to be qualified as a new active substance in itself.

4. Orphan medicinal products

According to the conclusion of the COMP (Opinion dated 06/06/2010) the prevalence of the "condition" multiple myeloma is 2.2 per 10000 individuals in the EU.

5. Benefit risk assessment

Benefits

Beneficial effects

The Applicant has submitted adequate evidence to support the beneficial effect of high dose oral dexamethasone in combination with other agents, for the treatment of symptomatic multiple myeloma, both in the first line and relapsed setting. The recommended daily dose is 40 mg once daily for many regimens. Therefore the availability of a 40 mg strength tablet for the first time will benefit patients, who are currently required to take multiple lower strength dexamethasone tablets, in addition to other agents. A survey conducted among members of a French multiple myeloma patient organization has demonstrated that patients largely prefer a single tablet of dexamethasone to all other dosage forms.

Based on data from a single comparative bioavailability study CPA 402-11, the AUC of Neofordex was comparable to an appropriate reference product. The Applicant has provided relevant non-clinical *in vitro* data, and a literature-based discussion, to support the low relevance of the C_{max} value in the clinical efficacy of dexamethasone in multiple myeloma treatment. Given the obvious limitations to conduct a conventional comparative clinical trial in patients, the extrapolation of this non-clinical data to the clinical situation is considered acceptable.

Uncertainty in the knowledge about the beneficial effects

According to the proposed posology, and supported by some literature reports, a significant proportion of patients will require 20 mg dexamethasone daily. A 20 mg strength tablet would avoid the need to break tablets. A post-authorisation measure to develop a 20 mg strength tablet is proposed.

Risks

Unfavourable effects

The safety profile of dexamethasone, which has been in clinical use for many years, is well known. The applicant has updated the safety profile, considering use at high dose and in combination, for the treatment of symptomatic multiple myeloma. The safety profile of dexamethasone 40 mg daily as pulse therapy is judged acceptable.

Uncertainty in the knowledge about the unfavourable effects

The anhydrous drug substance has potential to impact bioavailability. With regard to the drug product, the proposed, revised dissolution method has not yet been demonstrated to be discriminatory. Thus, changes to dissolution performance with potential to impact bioavailability may not be detected during routine batch analysis.

Stability data generated using the revised dissolution method has highlighted a marked decrease in rate and extent of release with time and temperature. The mechanism underlying this change has not yet been established. In light of these changes, there is insufficient stability data to assure the revised, proposed shelf-life and temperature storage conditions of 12 months at not more than 25°C.

Benefit-risk balance

The benefits of Neofordex 40 mg Tablet for the treatment of adults with symptomatic multiple myeloma are outweighed by uncertainty regarding controls of the drug substance, the adequacy of the proposed dissolution method and lack of assurance of product stability over the proposed shelf-life of 12 months at not more than 25°C.

5.1. Conclusions

The overall B/R of Neofordex 40 mg Tablets is negative.