SCIENTIFIC DISCUSSION

1.1 Introduction

Multiple myeloma is a B-cell malignancy of the plasma cell and represents the second most common haematological malignancy (about 10%), with non-Hodgkin's lymphoma being the most common. It is estimated that approximately 21,500 new cases of multiple myeloma are diagnosed per annum with approximately 16,000 deaths from the disease annually within the EU (EUCAN database, 1998).

Multiple myeloma is characterised by an asymptomatic or subclinical phase before diagnosis (possibly for several years), a chronic phase lasting several years and an aggressive terminal phase. Multiple myeloma is primarily a disease of the elderly, with a median age at diagnosis of 68 years (Sirohi and Powles, 2004). Multiple myeloma leads to progressive morbidity and eventual mortality by lowering resistance to infection and causing significant skeletal destruction (with bone pain, pathological fractures, and hypercalcaemia [Kyle and Rajkumar, 2004]), anaemia, renal failure, and, less commonly, neurological complications and hyperviscosity. From the time of diagnosis, the survival without treatment is between 6 to 12 months and extends to 3 years with chemotherapy. Approximately 25% of patients survive 5 years or longer, with fewer than 5% surviving longer than 10 years.

At the time of diagnosis, multiple myeloma is a heterogeneous disease, with a course that varies on the basis of both disease- and host-related factors (e.g., age, renal function, stage, alpha 2-microglobulin, chromosomal abnormalities). Most patients with myeloma receive multiple treatments over the course of their disease, and the precise sequence of therapy and regimens used can be quite variable.

Though the treatment for multiple myeloma has changed dramatically within the last decade, the disease remains incurable. Approved anticancer agents for the treatment of myeloma in the US include melphalan (1992), carmustine (BCNU, 1977) and cyclophosphamide (1959) and in addition, in Europe, epirubicin is also approved for treatment of this disease.

Spontaneous remissions do not occur in multiple myeloma and no placebo effect on response has been noted. Standard therapy for myeloma currently has consisted of 4 classes of agents: corticosteroids, alkylating agents, anthracyclines, and investigational agents. A fifth treatment class available to patients under the age of 65 years is high-dose chemotherapy and bone marrow transplantation.

Currently, a medicinal product containing bortezomib, a proteasome inhibitor has been approved in the EU for the treatment of patients with multiple myeloma whose disease has relapsed after at least one prior treatment and who have already undergone or are unsuitable for transplantation. In an open-label, single-arm, multicentre, non-randomised study of 202 patients, the overall response rate to bortezomib was 35% (67/193), with the response lasting for a median time of 12 months (Richardson *et al*, 2003). One randomised study included 669 with relapsed/refractory myeloma patients to receive either an intravenous bolus of bortezomib or pulsed high-dose dexamethasone. Time-to-disease progression (TTP) was significantly longer in the bortezomib group compared to the dexamethasone group (189 vs. 109 days) (Richardson *et al*, 2005). A significantly higher incidence of serious adverse events was observed with bortezomib in comparison to dexamethasone (Dispenzieri *et al*, 2005).

Resistance to conventional treatments is a major problem resulting in relapse and in order to overcome treatment resistance, novel approaches are required to target the mechanisms by which myeloma cells proliferate and survive in the bone marrow (Richardson *et al*, 2002).

Lenalidomide is one of a number of novel compounds based on the molecular structure of thalidomide that have been developed with a view to improving the immunomodulatory effect of the parent compound whilst also providing a better safety profile (Bartlett *et al*, 2004, Richardson *et al*, 2002).

Celgene Europe Ltd. has applied for a marketing authorisation through the centralised procedure for the medicinal product Revlimid 5, 10, 15 and 25 mg hard capsules, containing respectively 5, 10, 15 and 25 mg of the new chemical entity lenalidomide. Lenalidomide is an immunomodulating agent.

1.2 Quality aspects

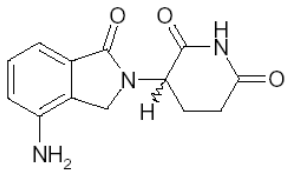
Introduction

Revlimid has been developed as hard capsules in 4 dosage strengths of 5, 10, 15 and 25 mg. Revlimid capsules are supplied in PVC/ACLAR (PCTFE) blisters with push through aluminium foil.

Active Substance

- Manufacture

Lenalidomide (3-(4' aminoisoindoline-1'-one)-1-piperidine-2, 6-dione) is a new chemical entity.



It is a synthetic derivative of glutamic acid and is structurally close to thalidomide (identical backbone but differs from thalidomide by removing an oxygen from the phthalyl ring and by adding an amine group). Although it is chiral and possesses an asymmetric carbon, it has been developed as a racemic mixture since it undergoes racemisation under physiological conditions. It is obtained as a hemihydrate form and is non-hygroscopic.

Lenalidomide exhibits the phenomenon of polymorphism but the commercial process leads only to the desired polymorph.

Lenalidomide synthetic process consists of 4 steps starting from alpha-aminoglutarimide hydrochloride and methyl 2-bromomethyl-3-nitrobenzoate. The process can be summarised as follow: coupling step, reduction step (crude lenalidomide), recrystallisation (pre-micronised lenalidomide) and micronisation.

The route of synthesis has been sufficiently described including the comprehensive description of the micronisation step.

Appropriate specifications have been provided for the intermediates, starting materials, reagents, solvents and auxiliary materials. However, minor points will be addressed further through follow-up measures.

Adequate in-process controls for critical steps and intermediates have been applied during the synthesis of lenalidomide. In addition, validation of the process has been performed for the lenalidomide synthesis and will be completed in follow-up measures. Analytical methods have been sufficiently described and validated.

The structure of lenalidomide has been fully elucidated using usual methods such as elemental analysis, IR (infra-red), UV (ultra-violet), mass spectrometry, ^{1}H-NMR (nuclear magnetic resonance), ^{13}C-NMR spectroscopy, X-ray, optical rotation, DSC (differential scanning calorimetry), TGA (thermal gravimetric analysis), and particle size analysis. Analyses were especially focused on the polymorphism of the molecule as well as the particle size.

Potential impurities, degradation products and residual solvents which may be found in lenalidomide have been extensively discussed. Impurities remain below the ICH qualification limits (guideline ICH Q3A).

Batch analysis data of 20 lots of lenalidomide are within the specification. The level of impurities and residual solvents remain very low and do not exceed ICH qualification thresholds.

- Specification

Since lenalidomide is not described in any pharmacopoeia, an in-house monograph has been presented. Specifications for lenalidomide (hemihydrate) include parameters such as appearance, identification (IR and X-ray diffraction), assay (HPLC), related impurities (HPLC), residual solvents (GC), water content (Karl-Fischer), heavy metals, sulphated ash and particle size (laser diffraction).

Specification is appropriately described and justified for residual solvents and particle size limits. Limits retained are in line with the ICH guidelines.

Analytical methods have satisfactorily described and validated.

Lenalidomide is packaged in double low-density polyethylene (LDPE) bags, placed in high-density polyethylene (HDPE) drums. The packaging materials comply with relevant EC directives and Ph Eur. monographs.

- Stability

Stability studies have been conducted on 3 pilot batches of lenalidomide stored in the commercial packaging under ICH conditions (up to 24 months at 25°C/60% RH and 6 months at 40°C/75% RH). Tested parameters tested included: visual appearance, assay, related impurities, X-ray powder diffraction and water content.

All results remain well within the retained specification under long-term and accelerated conditions. Moreover, photostability stability testing indicated that lenalidomide is not light sensitive.

Based on the available data, a retest period of 2 years was granted providing that the active substance is kept in the commercial packaging and not above 25°C. The applicant has committed to continue the studies.

Medicinal Product

- Pharmaceutical Development

Active Substance: The pharmaceutical development has taken into consideration the main aspects of the active substance: particle size and polymorphic form.

Formulation Development: A hard capsule dosage form was chosen due to its favourable performance in manufacturing studies and analytical testing. Revlimid capsules, 5 and 10 mg, are dose proportional and use a common blend whereas the 15 and 25 mg are slightly different for the ingredients ratio. Formulation development is sufficiently detailed. Micronisation has been performed to ensure blend and content uniformity of the active substance present at a low level in the medicinal product formulation.

Overages: No overage is included in the formulation for Revlimid capsules 5, 10, 15 and 25 mg.

Physicochemical and Biological Properties: The impact of physicochemical properties (particle size and polymorphic form) of lenalidomide that could theoretically affect the performance of the medicinal product has been studied. It can be concluded that neither the particle size (when included in the distribution range of micronised particles), neither does the polymorphic form affect the dissolution of the capsules.

Manufacturing Process Development: The manufacturing process is a simple blending and filling process. The manufacturing development has been adequately described.

Container closure system: Revlimid capsules, 5, 10, 15 and 25 mg are packaged in blisters (PVC/ACLAR) with push-through foil. Suitability of the material is demonstrated by the stability data.

Excipients: The excipients selected for the lenalidomide capsules formulation are those typically used in capsule formulations. They are all described in Ph. Eur. and comply with the corresponding monographs, and include anhydrous lactose (as diluent), microcrystalline cellulose (as diluent), croscarmellose sodium (as disintegrant) and magnesium stearate (as lubricant).

Regarding the capsule shells, adequate manufacturer's specification includes testing for appearance, colour, loss on drying, disintegration time, identity of gelatin, microbiological tests as per Ph Eur. and physical dimensions. The components of the printing inks are in compliance with Ph Eur. or USP/NF. In addition, the hard capsule colorants comply with the relevant EC Directives on colorants in foodstuffs.

Compatibility between the active substance and the excipients has been suitably demonstrated.

- Adventitious Agents

Among the excipients used in the formulation, only lactose (ingredient of the formulation) and gelatin (component of the capsule shell) are from animal origin. However, lactose is sourced from healthy animals under the same conditions as milk collected for human consumption (EMEA 410/01 rev 1) and TSE declaration is provided in 3.2.R. TSE certificates from the gelatin suppliers are provided.

- Manufacture of the Product

The manufacturing process is simple and consists of dry blending of the ingredients and filling the capsules. The process is considered standard as per the guideline CHMP/QWP/848/99. It has been adequately described including the equipment and the operating parameters. Appropriate in-process controls of the critical steps and intermediates have been set, such as control of the fill weight of the capsules.

Validation of the manufacturing process has been carried out satisfactorily at both manufacturing sites. However minor points will be resolved through follow-up measures.

- Product Specification

The proposed specifications at release and at the end of shelf life for Revlimid 5, 10, 15 and 25 mg capsules include appearance, identification (HPLC and UV), assay of the active substance (HPLC), related substances (HPLC), dissolution (HPLC), uniformity of dosage units (Ph Eur. 2.9.40) and microbial contamination (Ph Eur. 5.1.4 category 3A). Specification has been correctly justified.

Non-compendial analytical methods have been described and validated in accordance with ICH requirements.

Batch analyses data confirm the consistency of the manufacturing process. All the results comply with the retained specifications.

Container closure system: Revlimid capsules, 5, 10, 15 and 25 mg, are packaged in blisters (PVC/ACLAR) with push-through foil. The packaging material has been adequately characterised and complies with Ph Eur. 3.1.11.

- Stability of the Product

Stability studies have been conducted on 4 batches (pilot and commercial-scale) of each strength (5, 10, 15 and 25 mg) kept in the commercial packaging under ICH conditions (up to 24 months at 25°C/60% and 6 months at 40°C/75% RH). Tested parameters include appearance, assay, related impurities and dissolution.

All the results remain within the specification. Even under accelerated conditions the medicinal product is stable and no significant trend is observed except for a few out of specification results at 40°C/75%. A photostability study has showed that the finished medicinal product is not light sensitive.

The applicant has committed to continue the stability studies.

Discussion on chemical, pharmaceutical and biological aspects

Generally, satisfactory documentation has been provided. The active substance is well characterised and the retained specification including the impurities levels. Lenalidomide is stable and stability data support the proposed re-test period providing that the active substance is kept in the commercial packaging and not above 25°C.

Regarding the finished medicinal product, the manufacturing process is a standard process. It is adequately described and controlled. It should ensure a consistent quality for the medicinal product. Appropriate specification has been selected for these hard-capsules. Stability studies under ICH conditions have demonstrated the good stability of the finished medicinal product. Stability data support the proposed shelf life and storage conditions as defined in the Summary of Product Characteristics (SPC). At the time of the CHMP opinion, there were some outstanding quality issues with no impact on the benefit/risk. The applicant undertook to provide with the necessary information as follow-up measures within an agreed timeframe and to submit variations if required following the evaluation of this additional information.

1.3 Non-clinical aspects

Introduction

Pivotal toxicity studies have been performed in rats, monkey and rabbits (embryo-foetal toxicity). Studies on pharmacokinetics, toxicokinetics and toxicology were performed in compliance with Good Laboratory Practice (GLP).

Pharmacology

The pharmacological properties of lenalidomide were characterised in non-GLP *in vitro* and *in vivo* studies focussing on effects on erythropoiesis, haematopoietic tumours, angiogenesis, T-cell proliferation, cytokine stimulation, and NK activity.

- Primary pharmacodynamics

Based on *in vitro* and *in vivo* tests, lenalidomide has been shown to:

- inhibit secretion of pro-inflammatory cytokines TNF-α, IL-1β, IL-6 and IL-12 and increases the secretion of anti-inflammatory cytokine Il-10 by monocytes
- induce T-cell proliferation and IL-2 and IFN-γ production, and enhances NK cell activation
- inhibit the proliferation of various haematopoietic tumour cell lines, particularly the multiple myeloma
- enhance foetal haemoglobin expression upon CD34+ erythroid stem cell differentiation
- inhibit processes of angiogenesis including endothelial cell migration and tube formation
- inhibit the growth of haematopoietic tumour cells and, by inhibiting angiogenesis, reduce the growth of solid tumours *in vivo*.

The molecular target of lenalidomide is not known.

- Secondary pharmacodynamics and safety pharmacology

The complete core battery of safety pharmacology tests, following ICH guidance, was performed, to determine neuro-behavioural, cardiovascular and respiratory effects. The effects of lenalidomide on

general activity and behaviour were evaluated *in vivo*, in the rat model system. The potential for cardiovascular effects was evaluated *in vivo* (beagle dogs) and *in vitro* (HEK-293 cell line), while *in vivo* respiratory function was assessed in anaesthetised beagle dogs. No relevant effects were observed.

- Pharmacodynamic drug interactions

Several *in vitro* pharmacodynamic drug interactions were performed, regarding the total effect on foetal haemoglobin, inhibition of rolipam-induced PDE4A4 foci, inhibition of cell proliferation, potentiation of NK activity and anti-tumour activity. Tested drugs were hydroxyurea, vincristine, rapamycin, paclitaxel, carboplatin, gemcitabine, cisplatin, and rituximab. Synergistic effects were observed with rapamycin in inhibition of cell growth and survival, with hydroxyurea in effects on foetal haemoglobin. One *in vivo* study was also performed in severe combined immunodeficiency mice where concurrent administration of lenalidomide and rituximab was more effective in controlling lymphoma growth and prolonging survival than rituximab therapy alone.

Pharmacokinetics

The pharmacokinetics of lenalidomide has been investigated in *in vitro* and *in vivo* studies. The significant findings of these studies are briefly presented below:

- The S and R enantiomers of lenalidomide are stable to racemisation during storage at -70^{o}C in buffered (acidic or neutral pH) plasma from rat, monkey and man. The enantiomers undergo significant non-enzymatic racemisation in plasma at 37^{0}C at neutral or alkaline pH
- Absolute oral bioavailability of lenalidomide is 68 %, 88 % and 50 % in rat, dog and monkey respectively
- The volume of distribution observed in all species tested indicated an extensive distribution into tissues
- The plasma protein binding is low in all species including humans (19% to 29%)
- The highest concentration of radioactivity following oral administration of [^{14}C]-lenalidomide to rat was in the kidney. Distribution to the brain was extremely low. Distribution to the foetus was limited after oral administration to pregnant rats
- Lenalidomide is metabolically stable *in vitro*, metabolism related to hydrolysis is seen *in vivo*
- Lenalidomide does not inhibit any of the major cytochrome P450 (CYP) isozymes *in vitro*
- The elimination half-life in rats and monkeys was approximately 2 hours and 13 hours, respectively, after a single oral administration
- Lenalidomide excretion occurs mainly via the urine. The major component in the urine in humans, rats and monkeys is the parent compound

Toxicology

- Single dose toxicity

Acute dose (40 and 2000 mg/kg) toxicology studies in mice and rats via intravenous and oral administration respectively, were conducted. No mortality was observed at either dose.

- Repeat dose toxicity (with toxicokinetics)

The potential toxicity of lenalidomide was assessed after repeated administration to rats (up to 26 weeks duration) and monkeys (up to 52 weeks duration).

Repeated oral administration of 75, 150 and 300 mg/kg/day to rats for up to 26 weeks produced a reversible treatment-related increase in kidney pelvis mineralisation in all 3 doses, most notably in females. The no observed adverse effect level (NOAEL) was considered to be less than 75 mg/kg/day, and is approximately 25-fold greater than the human daily exposure based on AUC exposure.

Repeated oral administration of 4 and 6 mg/kg/day to monkeys for up to 20 weeks produced mortality and significant toxicity (marked weight loss, reduced red and white blood cell and platelet counts, multiple organ haemorrhage, gastrointestinal tract inflammation, lymphoid organs and bone marrow

atrophy). Repeated oral administration of 1 and 2 mg/kg/day to monkeys for up to 1 year produced reversible changes in bone marrow cellularity, a slight decrease in myeloid:erythroid cell ratio and thymic atrophy. The NOAEL is less than 1 mg/kg. Mild suppression of white blood cell count was observed at 1 mg/kg/day corresponding to approximately the same human dose based on AUC comparison.

- Genotoxicity

An extensive battery of genotoxic studies was conducted, including the ICH guidelines for testing of genotoxic potential (a bacterial mutation test, a mouse lymphoma assay, a cultured human peripheral blood lymphocyte test, a Syrian hamster embryo transformation assay, and an *in vivo* rat micronucleus tests. There were no indications of genotoxicity in any of these assays. However, genotoxicity assays were performed without knowing the level of two impurities, namely RC3 and RC4. This aspect will be investigated in the post-authorisation phase (follow-up measure).

- Carcinogenicity

No studies on carcinogenicity have been performed which is acceptable for the proposed indication.

- Reproduction toxicity

A complete battery of ICH recommended reproductive/developmental toxicology studies was conducted, including studies to assess the potential adverse effects on male and female fertility and reproduction, embryo-foetal development (embryo-foetal toxicity/teratogenicity) and maternal reproductive performance and peri- and post-natal development of the offspring.

Doses of lenalidomide as high as 500 mg/kg/day did not selectively affect male or female rat reproductive performance or embryonic viability during early embryogenesis.

In the developmental toxicity study in the rats, the maternal and developmental NOAEL were 300 mg/kg/day, with threshold maternal and developmental toxicity at 500 mg/kg/day. Foetal viability was unaffected and there were no embryo-foetal alterations attributable to lenalidomide.

In rabbits, administered 3, 10 and 20 mg/kg/day orally corresponding to up to 6 times the human exposure, no limb abnormalities were attributable to lenalidomide. Developmental toxicity at the 10 and 20 mg/kg/day dose levels was characterised by slightly reduced foetal body weights, increased incidences of post implantation loss (early and late resorptions and intrauterine deaths), and gross external findings in the foetuses associated with morbidity and pharmacotoxic effects of lenalidomide (purple discoloration of the skin on the entire body). An absence of the intermediate lobe of the lung was observed at 10 and 20 mg/kg/day with dose dependence and displaced kidneys were observed at 20 mg/kg/day. Although it was observed at maternotoxic levels they may be attributable to a direct effect. The human relevance of these effects is not known. Soft tissue and skeletal variations in the foetuses were also observed at 10 and 20 mg/kg/day. These included minor variations in skull ossification (irregular nasal-frontal suture) and small delays in ossification of the metacarpals, associated with the reduced foetal body weights. In rabbits, the maternal and developmental NOAEL for lenalidomide were 3 mg/kg/day corresponding to a safety margin of 1.3 considering a 25 mg/day therapeutic dose.

In some of the rabbit of studies, thalidomide was included as a positive control for teratogenicity. Thalidomide showed the expected teratogenicity and the NOAEL for developmental toxicity was estimated to be 20 mg/kg in a rabbit strain. While the observed foetal alterations in most cases affected the limbs, it should be stressed that they are distinct from the known foetal alterations occurring in humans.

The CHMP requested additional investigations to better characterise the potential embryotoxic and teratogenic effects of lenalidomide. Studies with thalidomide in monkeys have shown a relative predictive value in teratogenicity to what has been documented in humans, both in terms of doses and types of malformation. The toxicological studies with lenalidomide in cynomolgus monkeys have shown similar toxicity (at similar exposure levels) to what has been documented in patients. Therefore,

cynomolgus monkeys appear to be highly relevant for the evaluation of both pharmacology and toxicology of lenalidomide. The applicant has committed to perform a study on embryo-foetal toxicity as a post-approval commitment in a sensitive species.

In the pre- and post-natal developmental toxicity study of lenalidomide in the rat, there were no adverse effects on the viability, growth or behaviour of the offspring. The NOAEL for development of the offspring was 500 mg/kg/day.

- Local tolerance

No local tolerance studies have been performed with lenalidomide.

- Other toxicity studies

No specific immunotoxicological programme has been performed with lenalidomide.

Ecotoxicity/environmental risk assessment

The Environmental Risk Assessment (ERA) for lenalidomide has been provided in compliance with the requirements of Directive 2001/83/EC as amended.

The predicted surface water concentration for lenalidomide indicates that its use in the proposed indication should pose a negligible risk to the environment. Should any lenalidomide reach the environment through disposal of unused product, the environmental risk is likely to be minimal owning to the drug's low inherent toxicity and absence of bioaccumulation potential. As with all unused medications, appropriate disposal procedures should be employed.

Discussion on non-clinical aspects

Pharmacology

Lenalidomide has shown activity in a number of model systems. The pharmacology studies suggest that the therapeutic activities of lenalidomide fall into the following categories: anti-inflammatory, immunomodulatory, anti-proliferative, anti-angiogenic and pro-erythropoietic. These partly paradoxical findings make impossible to predict the effect of lenalidomide in more complex in vivo models and in human disease. The molecular target of lenalidomide remains unknown for any cell type. In vivo, lenalidomide was shown to delay tumour growth and prolong survival in a mouse xenograft model with human lymphoma cells. Lenalidomide showed effect on solid tumour cell growth in two mouse models. Inhibition of angiogenesis was demonstrated in an in vivo model in the rat. The lack of molecular understanding has several consequences for the assessment of the clinical usefulness. It limits the possibility to predict unwanted pharmacological events, and it makes difficult to evaluate the relevance of different animal species for the safety assessment.

Lenalidomide has been developed based on the structure and pharmacology of thalidomide. In vitro data suggest that lenalidomide is much more potent. Lenalidomide was 10-1000 times more potent than thalidomide in various in vitro pharmacology studies of immunomodulatory, anti-proliferative, and pro-erythropoietic activities. However, the data give no evidence for a qualitative difference in pharmacology. This is a key issue, since the broad pharmacology of these compounds is most likely the basis for the safety issues which have arisen. This is particularly true for the probably most important safety concern, namely the teratogenicity of thalidomide. This issue will be discussed further below.

Safety pharmacology studies in rat, dog and monkey gave no evidence for safety risks. However, based on the data from toxicology studies in the rat the relevance of the rat for safety assessment is questionable. The lack of hERG channel inhibition, lack of cardiovascular findings in the dog safety pharmacology study and in the monkey repeat dose toxicity study do give some reassurance that lenalidomide is devoid of cardiovascular effects.

Pharmacokinetics

Lenalidomide is rapidly absorbed after oral administration in rats and monkeys. Bioavailability varies between 50-75%. The elimination half-life in rats and monkeys is approximately 2 and 13 hours, respectively, after a single oral administration. In humans, terminal half-life is dependent on dose (3.2 hours at 5 mg and 8.7 hours at 400 mg). Lenalidomide is widely distributed with a high volume of distribution. In a whole body autoradiography study in the rat, tissues levels were comparable to the plasma values. In pregnant animals, distribution to the foetus was observed.

In vitro metabolism studies showed no evidence for metabolism of lenalidomide. In vivo, metabolites formed by hydrolysis were observed. However, it was apparent that such hydrolysis products were formed *ex vivo* and the presented data did not allow a clear estimate of in vivo hydrolysis. A comparison of data from different studies with labelled lenalidomide vs. non-labelled lenalidomide suggests that a vast majority of the administered product is present as intact lenalidomide in plasma. Lenalidomide is produced as a racemic mixture of two enantiomers. Individual enantiomers were shown to undergo significant non-enzymatic racemisation in human plasma (complete after 6 hours).

After intravenous administration in rats and monkeys, the majority of the compound was excreted in urine, while after oral administration equal amounts were found in urine and faeces. This suggests that renal elimination is the main excretion path, while after oral dosing a substantial part is not absorbed and found in the faeces. There are no data on excretion in milk or in semen. For thalidomide, excretion in semen has been demonstrated and measures have been taken to protect women from exposure during sexual intercourse with patients taking thalidomide. Data on the presence of lenalidomide in semen are required in order to take a decision whether similar measures should be introduced for lenalidomide.

Toxicology
The primary toxicities observed after repeated oral administrations of lenalidomide were associated with the haematopoietic lympho-reticular systems and the kidneys, generally reversible after a 4- to 7-week recovery period. Rats appeared to be more sensitive to the effects on the kidneys, while cynomolgus monkeys were more sensitive to the effects on the haematopoietic systems. The NOAEL for rats in the chronic 26-week toxicity study was set at < 75 mg/kg/day. Based on AUC comparison, this dose was approximately 25-fold greater than the human daily exposure. In repeated-dose toxicity studies in monkeys, NOAEL is less than 1 mg/kg; this dose was equivalent to the human daily exposure (safety margin: 0.95 to 1).

The findings in monkey are likely to be a consequence of the pharmacological effect of lenalidomide and show similarity to what has been seen in the clinic, where neutropenia and thrombocytopenia were the most common adverse effects. The findings in the rat and the monkey underline the striking species differences in pharmacology and toxicology of lenalidomide, and it is concluded that the monkey but not the rat is a relevant species for safety evaluation.

For the non-clinical safety evaluation it is not possible to reach any conclusion on safety profile of Revlimid compared to thalidomide.

Lenalidomide showed no evidence for genotoxicity. Further *in vitro* characterisation of the genotoxicity of the active substance including impurities will be performed as a follow-up measure.

No studies on carcinogenicity have been performed which is acceptable for the proposed indication.

The most important issue for the non-clinical assessment of lenalidomide safety is reproductive and developmental toxicity, given the structural and pharmacological similarities with thalidomide. Studies on fertility and early embryonic development and on pre-natal and post-natal have been performed in the rat. These studies showed no evidence for important toxicity but the relevance and sensitivity of the rat is questionable as the presented data on general toxicity of lenalidomide show minimal toxicity in this species.

Embryo-foetal development has been studied in rats and rabbits. The rat study showed no evidence of toxicity, but the rat species is not considered as a relevant model for thalidomide analogues as it is poorly susceptible to thalidomide teratogenicity.

In the rabbit, lenalidomide exhibited foetal toxicity with increased post-implantation loss, decreased foetal weight, and also an increased frequency of foetal alterations (absence of the intermediate lobe of the lung and displaced kidneys). Lenalidomide did not induce, in particular, any limb malformations in the rabbit.

Based on the structural and pharmacological similarity to thalidomide and the foetal alterations observed in the rabbit study, lenalidomide has to be contraindicated during pregnancy, and precautions should be taken for women of childbearing potential.

The embryotoxic and teratogenic potential of lenalidomide will be further characterised in a sensitive species (follow-up measure).

1.4 Clinical aspects

Introduction

Lenalidomide, at the dose of 25 mg/day in combination with dexamethasone (40 mg/day) is indicated for the treatment of patients with relapsed or refractory multiple myeloma who have received at least one prior therapy. Lenalidomide 25 mg/day is taken orally on days 1 to 21 of each 28-day cycle, and 40 mg/day of dexamethasone on Days 1 to 4, 9 to 12 and 17 to 20 of each 28-day cycle for the first 4 cycles, with reduction to 40 mg/day of dexamethasone on days 1 to 4 of each cycle thereafter.

Table 1 Clinical studies

Study Number	Description	Population	Number of subjects/patients
Non-Clinical Pharmacology studies on human biomaterials			
1398/295	Study to determine extent of *in vitro* binding of (^{14}C)-lenalidomide to plasma proteins in rat, rabbit, monkey and human (both healthy volunteers and myeloma patients)	N/A	N/A
1398/199	Investigation of effects of lenalidomide on selected cytochrome P450 activities in human liver microsomes: prediction of drug interactions	N/A	N/A
1398/208	Identification of the human P450 isozymes involved in the metabolism of lenalidomide	N/A	N/A
1398/335	Identification of the cytochrome P450 enzymes responsible for the *in vitro* metabolism of (^{14}C)-lenalidomide in human liver microsomes	N/A	N/A
1398/348	Investigation of *in vitro* metabolism of (^{14}C)-lenalidomide in isolated human hepatocytes	N/A	N/A
Clinical pharmacology studies			
1398/142	A Phase I, single-blind, placebo-controlled, ascending single oral dose, safety, tolerability and pharmacokinetic study in healthy male subjects incorporating a comparison of fed/fasted kinetics	Healthy volunteers	19
1398/180	A Phase I, single-blind, placebo-controlled, multiple oral dose, safety, tolerability, pharmacodynamic and pharmacokinetic study in healthy male subjects	Healthy volunteers	8
CDC-501-001	A Phase I/II, open-label, non-randomised, dose-escalation safety and pharmacokinetics study intended to find a maximum tolerated dose (MTD)	Patients with relapsed or refractory multiple myeloma (MM)	27
CC-5013-PK-001	The Pharmacokinetics of A Single, Oral 25 mg dose of Revlimid (CC-5013) in Patients with Impaired Renal Function	Healthy volunteers and renal impaired subjects	30
CC-5013-PK-003	A healthy volunteer drug interaction study of Revlimid with warfarin	Healthy volunteers	18
CC-5013-PK-004	A healthy volunteer drug interaction study of Revlimid with digoxin	Healthy volunteers	19

Study Number	Description	Population	Number of subjects/patients
Clinical studies			
CC-5013-MM-007	A Phase II, multicentre, controlled, parallel-group, randomised, open-label study of lenalidomide monotherapy (30 mg/day either bid or qd) in patients with relapsed or refractory multiple myeloma	Patients with relapsed or refractory MM	102
CC-5013-MM-014	A Phase II, multicentre, single-arm, open-label study of lenalidomide monotherapy (30 mg/day) in patients with relapsed or refractory multiple myeloma	Patients with relapsed or refractory MM	222
CC-5013-MM-009 CC-5013-MM-010	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	Patients with relapsed or refractory MM	353 351

GCP

According to the applicant, all studies were conducted following appropriate Good Clinical Practice guidelines and considerations for the ethical treatment of human subjects. The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Pharmacokinetics

The analytical method used for the detection of lenalidomide in blood and urine samples is a liquid chromatography method with tandem mass spectrometric detection (LC-MS/MS). These methods were properly validated and associated with satisfactory lower limits of quantitation.

- Absorption

Absolute bioavailability has not been determined in humans. However, results from animal studies and clinical pharmacokinetics show that absorption is linear and rapid. Lenalidomide can be taken either before or after food, taking into consideration that co-administration with food delays absorption of the active substance.

- Distribution

The binding of radiolabelled "semi-racemic" lenalidomide to human plasma proteins was investigated *in vitro* by ultrafiltration at concentrations of 30-10000 ng/ml. The mean binding was 23 and 29% in plasma from myeloma patients and healthy volunteers, respectively. No concentration dependency was observed. The apparent oral volume of distribution was different between doses and studies but may be in the order 50-200 l.

- Elimination

Lenalidomide is not metabolised via cytochrome P450 in humans and further enzymatic systems have not been studied. The excretion of lenalidomide via the renal pathway is high, with the overall urinary recovery of unchanged drug being approximately 85% of the administered single oral dose. Urinary excretion of lenalidomide is approximately 27% lower when lenalidomide is administered in the fed condition compared to fast condition. Renal clearance was at least 190 ml/min, suggesting that active renal secretion occurs.

In vitro studies investigating which transporters are involved in the active renal secretion of lenalidomide are ongoing. The applicant committed to submit the results of mass-balance 14C study.

- Dose proportionality and time dependencies

The pharmacokinetic disposition of lenalidomide is linear in healthy volunteers and patients. The maximum concentration (C_{max}) and area-under-the-curve (AUC) increased in a dose-proportional manner over the dose range studied (5 to 400 mg).

There is no clinically important time- or dose-dependency in the pharmacokinetics of lenalidomide when administered to healthy volunteers or patients with relapsed multiple myeloma.

- Special populations

No formal studies have been conducted to assess the effects of age, gender, race or hepatic impairment on the pharmacokinetics of lenalidomide.

Study CC-5013-PK-001 studied the pharmacokinetics of lenalidomide after a single 25 mg oral dose under fasting conditions in subjects of different degrees of renal function and in patients with end stage renal disease (ESRD) receiving haemodialysis as follows:

Renal Function Groups

Group	N	Description	Measured Creatinine Clearance (CLcr)
1	7	Normal renal function	> 80 ml/min
2	5	Mild renal impairment (RI)	50 ≤ CLcr ≤ 80 ml/min
3	6	Moderate RI	30 ≤ CLcr < 50 ml/min
4	6	Severe RI	< 30 ml/min but not on dialysis
5	6	End Stage Renal Disease (ESRD)	Requiring dialysis

Subjects with ESRD received 2 single 25 mg doses at least 7 days apart: 1 dose was on a non-dialysis day and one 3 hours before a 4-hour haemodialysis period

Table 2 presents the pharmacokinetic parameters.

Table 2: Pharmacokinetic parameters

Mean (SD)	Renal Function Group					
	Normal (N = 7)	Mild RI (N = 5)	Moderate RI (N = 6)	Severe RI (N = 6)	ESRD (off dialysis) (N = 6)	ESRD (on dialysis) (N = 6)
C_{max} (ng/ml)	605 (246)	691 (110)	592 (177)	765 (81.3)	552 (140)	385 (112)
t_{max} (h) median (min-max)	1.00 (0.500, 2.00)	1.00 (1.00, 1.00)	1.00 (0.500, 1.50)	1.50 (0.500, 2.00)	1.25 (1.00, 2.00)	2.00 (0.500, 6.00)
AUC_t (ng.h/ml)	2065 (673)	2659 (1084)	5713 (744)	7872 (1312)	10501 (2048)	6310 (1018)
AUC_∞ (ng.h/ml)	2181 (703)	2767 (1094)	6021 (847)	8191 (1317)	11121 (2133)	6830 (919)
CL/F (ml/min)	207 (59)	166 (49)	71 (12)	52 (101)	39 (7)	62 (9)
Vz/F (l)	58 (15)	51 (13)	62 (15)	41 (8)	52 (8)	86 (14)
$t_{1/2}$,z (h)	3.34 (0.878)	3.67 (0.703)	10.6 (3.33)	9.22 (2.44)	15.6 (1.14)	16.1 (1.73)

A decrease in renal function resulted in an increase in total exposure (mean AUC_t and AUC_∞). C_{max} and t_{max} were not markedly affected by renal impairment. The exposure of the R and S-enantiomers were similarly affected by renal impairment. Subjects with normal renal function had higher mean % dose excreted unchanged in urine (85%), followed by subjects with mild RI (69%), subjects with moderate RI (42%) and subjects with severe RI (44%).

- Pharmacokinetic interaction studies

The potential for lenalidomide to cause drug-drug interactions was investigated *in vitro* and *in vivo*. A study to investigate the inhibitory effects of lenalidomide on the activities of selected P-450 cytochromes has been carried out *in vitro* to show that it is unlikely that lenalidomide causes metabolic drug interactions by inhibiting CYP activities. A study on the potential interaction of lenalidomide with p-glycoprotein is currently being completed.

Results from a chronic study in monkeys showed that lenalidomide at the dose of up to 2 mg/kg/day causes no notable effects on hepatic, microsomal protein or cytochrome P450 concentrations or on the activities of CYP1A, CYP2B, CYP2C, CYP3A, or CYP4A. Regarding the potential interaction with drugs having a high plasma-protein binding potential, the weak plasma-protein binding rate of lenalidomide (19%-29%) in all species including humans, makes the risk of drug-drug interactions related to displacement from plasmatic proteins, unlikely. However, formal clinical interaction studies have only been conducted for warfarin and digoxin, two frequently used drugs in the target population of patients. While no effect of lenalidomide on either enantiomer of warfarin was detected, there may

be a possible drug interaction between lenalidomide and digoxin, although it may not be clinically relevant.

In the recommended treatment regime, lenalidomide is administered with dexamethasone. Dexamethasone has been observed to induce metabolising enzymes in vivo in lower doses than recommended here. The degree of induction when dexamethasone is used in the recommended intermittent dose regime has not been studied. It may not be excluded that the dexamethasone component may give rise to reduced systemic exposure to concomitantly administered drugs which are metabolised by CYP or Phase II enzymes or transported by transport proteins. Due to the difficulties in performing a conclusive study, no *in vivo* study is requested. The risk of reduced levels of contraceptive steroids has been reflected in the SPC. An *in vitro* study of the possible inducing effect of lenalidomide is ongoing.

Warfarin
Co-administration of multiple doses of 10 mg of lenalidomide had no effect on the single dose pharmacokinetics of R- and S-warfarin. Co-administration of a single 25 mg dose of warfarin had no effect on the pharmacokinetics of lenalidomide. However, it is not known whether there is an interaction during clinical use (concomitant treatment with dexamethasone). Dexamethasone is a weak to moderate enzyme inducer and its effect on warfarin is unknown. Close monitoring of warfarin concentration is advised during the treatment.

Digoxin
Concomitant administration with lenalidomide 10 mg/day increased the plasma exposure of digoxin (0.5 mg, single dose) by 14% with a 90% CI (confidence interval) [0.52%-28.2%]. It is not known whether the effect will be different in the therapeutic situation (higher lenalidomide doses and concomitant treatment with dexamethasone). Therefore, monitoring of the digoxin concentration is advised during lenalidomide treatment.

- Pharmacokinetics using human biomaterials

No pharmacokinetic studies using human biomaterials have been conducted other than those already conducted to study pharmacokinetic interactions, namely: to determine extent of *in vitro* binding of (14C)-lenalidomide to plasma proteins, to determine the effect of lenalidomide on selected cytochrome P450 activities in human liver microsomes; to identify human P450 isoenzymes involved in the metabolism of lenalidomide and to investigate the *in vitro* metabolism of (14C)-lenalidomide in human hepatocytes.

Pharmacodynamics

- Primary and secondary pharmacology

Cytokine modulation: lenalidomide inhibits the secretion of pro-inflammatory cytokines including TNF-α, interleukin-1 beta (IL-1β), IL-6 and IL-12 and increases the secretion of anti-inflammatory cytokine IL-10 from peripheral blood mononuclear cells. In lipopolysaccharide (LPS)-stimulated PBMC, a dose-dependent inhibition for the following cytokines: TNF-α, IL-1β, IL-6, IL-12, MCP-1 and MIP-1α and a dose-dependent stimulatory effect on IL-10 were observed.

Induction of T-cell proliferation: lenalidomide elevates IL-2 and interferon-gamma (IFN-γ) production, and natural killer cell activities are induced. In anti-CD3 stimulated CD4+ T-cells, stimulation of IFN-γ, IL-2 and RANTES was observed. NK cell-mediated killing of tumour cells was more than doubled at 1 mg/ml.

Anti-proliferative effects: *in vitro*, lenalidomide inhibited proliferation of the MM cell line MM.1S and the Hs Sultan lymphoma cell. Lenalidomide also inhibited the proliferation of various haematopoietic tumour cell lines, in particular those with cytogenetic defects of chromosome 5, e.g., the Namalwa cell line.

Inhibition of angiogenesis: lenalidomide inhibits angiogenesis by blocking the formation of microvessels and endothelial cell tubes as well as the migration and adhesion of endothelial cells in *in vitro* angiogenesis models. In a human tissue culture model of angiogenesis, lenalidomide inhibited the microvessel formation emanating from an arterial explant in a dose-dependent manner.

Induction of foetal haemoglobin (HbF): lenalidomide enhances expression upon CD34+ haematopoietic stem cell differentiation in a model of erythroid progenitor differentiation. When CD34+ cells were cultured in the presence or absence of lenalidomide and hydroxyurea, alone or in combination, the induction of HbF production with lenalidomide was similar to that of hydroxyurea and there was a major synergistic effect when lenalidomide (10 μM) was combined with hydroxyurea, resulting in a striking reactivation of HbF.

Secondary pharmacology studies were conducted in two healthy volunteer PK-PD studies (Studies 1398/142 and 1398/180) and suggest that lenalidomide could have an effect on immune response.

Study 1398/142: lenalidomide appeared to have a possible effect on the immune response. An apparent dose-related decrease in CD4 count was observed at the higher dose levels of 200 mg lenalidomide (fasted and fed) and 400 mg lenalidomide (fasted) with the most pronounced effect occurring at 48-hour post-dose. In contrast, the CD8 count showed no treatment-related changes over time.

Study 1398/180: Multiple dosing with lenalidomide appeared to have an effect upon the immune response. An apparent dose-related decrease in both CD4 and CD8 blood counts was observed from Day 4 onwards. For CD4 counts, the magnitude of the decreases was relatively constant (approximately 300 /mm^3) on Days 4, 6 and 8, with values approaching baseline levels by the post-study assessment. By contrast, decreases in mean CD8 counts were most pronounced on Day 8 (242 /mm^3), with levels still considerably lower than the baseline value at the post-study assessment.

- Discussion on clinical pharmacology

The effects of age on the pharmacokinetics of lenalidomide have not been studied. Lenalidomide has been used in clinical trials in multiple myeloma patients up to 86 years of age. The percentage of patients aged 65 or over was not significantly different between the lenalidomide/dexamethasone and placebo/dexamethasone groups. No overall difference in safety or efficacy was observed between these patients and younger patients, but greater pre-disposition of older individuals cannot be ruled out. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and it would be prudent to monitor renal function.

Lenalidomide is substantially excreted by the kidney, therefore care should be taken in dose selection and monitoring of renal function is advised.

The following dose adjustments are recommended at the start of therapy for patients with impaired renal function.

Renal Function	Drug Dose Adjustment
Mild RI (80 > CLcr ≥ 50 ml/min)	25 mg (Full Dose) Every 24 hours
Moderate RI (30 ≤ CLcr < 50 ml/min)	10 mg[a] Every 24 hours
Severe RI (CLcr < 30 ml/min, not requiring dialysis)	15 mg Every 48 hours
ESRD (CLcr < 30 ml/min, requiring dialysis)	15 mg 3 times a week following each dialysis

[a] The dose may be escalated to 15 mg every 24 hours after 2 cycles if patient is not responding to treatment and is tolerating the drug

Studies to elucidate the lenalidomide anti-tumour effect like identifying and validating lenalidomide-binding proteins and developing a panel of lenalidomide-responsive cell models, independent of siRNA technology, are ongoing.

Since lenalidomide is mainly renally excreted unchanged, lenalidomide has not formally been studied in patients with impaired hepatic function and there are no specific dose recommendations.

No studies on the effects on the ability to drive and use machines have been performed. Lenalidomide may have minor or moderate influence on the ability to drive and use machines. Fatigue, dizziness, somnolence and blurred vision have been reported with the use of lenalidomide. Therefore, caution is recommended when driving or operating machines.

Clinical efficacy

The clinical efficacy and safety of lenalidomide has been investigated in one Phase I/II and in two Phase III clinical trials.

- Dose-response study(ies)

One single-centre, open-label, non-randomised Phase I/II, dose escalation study was conducted to determine the maximum tolerated dose (MTD) of orally administered lenalidomide in patients with refractory or relapsed multiple myeloma.

Four dose levels of 5, 10, 25 and 50 mg/day of lenalidomide were evaluated.

The MTD of lenalidomide was observed to be 25 mg/day. Myelosuppression was the primary adverse event associated with the administration of lenalidomide.

All 27 patients experienced at least one treatment-emergent AE. The most common AE were leucopenia (70.4%; 19/27) with 100% of patients at the 25-mg dose and thrombocytopenia (51.9%; 14/27). The incidence of Grade 3 or 4 neutropenia was 59.3% (85.7% at 50 mg/day). The incidence of Grade 3 or 4 thrombocytopenia was 29.6%.

Myelosuppression accounted for most of the adverse events that resulted in discontinuation from the study or in dose reduction (12 out of 13 patients).

- Main studies

Study CC-5013-MM-09 title: 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

Study CC-5013-MM-010 title: 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

METHODS

Study Participants

Selection criteria were similar for both studies: patients aged 18 years or older who had a prior or current Durie-Salmon Stage II or III multiple myeloma and who were considered to have disease progression after at least 2 cycles of anti-myeloma treatment or to have relapsed with progressive disease after treatment. Patients with measurable levels of M-paraprotein in serum (≥ 0.5 g/dl) or urine (≥ 0.2 g excreted in 24-hours collection sample) and an ECOG performance status of 0, 1, or 2 were eligible for the study. Patients could have been previously treated with thalidomide and/or radiation therapy, however, those with prior disease progression during high-dose dexamethasone were excluded.

Treatments

Patients were randomised to lenalidomide plus oral high-dose dexamethasone or placebo plus oral high-dose dexamethasone. Patients in the lenalidomide/dexamethasone group were administered 25 mg of lenalidomide orally once daily on Day 1 to 21 and a matching placebo capsule once daily on Day 22 to 28 of each 28-day cycle. Patients in the placebo/dexamethasone group took 1 placebo capsule on all days of the 28-day cycle. Patients in both treatment groups took 40 mg of dexamethasone orally once daily on Day 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 Day 1 to 4 every 28 days for the remaining cycles.

Objectives
The objective of these studies was to determine the efficacy and the safety of lenalidomide.

Outcomes/endpoints
The primary efficacy endpoint was time-to-progression (TTP) for both studies, calculated as the time from randomisation to the first documentation of progressive disease based on the myeloma response criteria developed by Bladé *et al*, or discontinuation from the treatment phase due to progressive disease according to the investigator, or death due to progressive disease during the treatment period.

Sensitivity analyses were also performed including progression-free survival (PFS), which was defined as the time from randomisation to documented progression (as defined above) or death due to any reason during the treatment period, whichever occurred first.

The secondary efficacy endpoints were overall survival (OS), the myeloma response rate, the time-to-first symptomatic skeletal-related events (SRE) and the time-to-first worsening in the Eastern Cooperative Oncology Group (ECOG) performance status.

Sample size
For TTP, a 50% improvement in median time-to-progression, from 6 months for dexamethasone alone to 9 months on the combination lenalidomide plus dexamethasone was considered as clinically relevant. With accrual of about 25 to 26 patients per month for 12 months for a total of 302 patients and a 9-month follow-up after the study closes to accrual, a one-sided log-rank test with an overall significance level of 0.025 would have 85% power to detect a hazard rate ratio of 1.5. Full information necessary for a log-rank test to have 85% power would be achieved when an event had been observed for at least 222 patients.

Randomisation
Patients in both studies were randomised in a 1:1 ratio to either the lenalidomide/dexamethasone group or the placebo/dexamethasone group.

Randomisation was stratified by the following prognostic factors:

- Baseline serum beta$_2$ (β_2)-microglobulin level ($\leq$ 2.5 mg/l versus > 2.5 mg/l)
- Prior therapy with high-dose chemotherapy supported by stem cell transplant (SCT) or no such prior therapy
- The number of prior anti-myeloma regimens (1 versus $\geq$ 1)

Blinding (masking)
The studies were double-blinded.

Statistical methods
An unstratified log-rank test was used as the primary test to compare survivorship functions for time-to-event variables in the 2 treatment groups. Exact test procedures for proportions were used to compare response rates.

In both studies, an interim analysis was planned when an event had been observed for 50% of the patients to determine if the study should be stopped for superiority, futility, or unfavourable toxicity.

The boundary for declaring superiority of one treatment group over the other was based on an alpha-spending function of the O'Brien-Fleming type.

RESULTS

Participant flow

Study MM-009: Three hundred fifty-three (353) patients were randomised (177 in the lenalidomide/dexamethasone group and 176 in the placebo/dexamethasone group).

Study MM-010: Three hundred fifty-one (351) patients were randomised (176 in the lenalidomide/dexamethasone group and 175 in the placebo/dexamethasone group). This study was amended to increase the sample size to 374 patients to gain additional safety data. In August 2004, the decision was made to suspend enrolment after 351 patients had been enrolled.

Table 3: Studies MM-009 and MM-010 - Patient disposition

	Study MM-009				Study MM-010			
	Len/Dex		Pbo/Dex		Len/Dex		Pbo/Dex	
Disposition	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Entered	177	100.0	176	100.0	176	100.0	175	100.0
Ongoing	63	35.6	13	7.4	55	31.3	19	10.9
Discontinued	114	64.4	163	92.6	121	68.8	156	89.1
Adverse Event	33	18.6	18	10.2	18	10.2	12	6.9
Progression of Disease	58	32.8	124	70.5	67	38.1	122	69.7
Lack of Therapeutic Effect	3	1.7	5	2.8	1	0.6	3	1.7
Patient Declined Further Participation	10	5.6	8	4.5	23	13.1	8	4.6
Death	4	2.3	1	0.6	11	6.3	10	5.7
Other	6	3.4	7	4.0	1	0.6	1	0.6

Recruitment

Study MM-009: Patients were enrolled from 11 February 2003 at 48 sites in the United States (44 sites) and Canada (4 sites). Data cut-off for the final study report was 28 June 2005 when the study was unmasked.

Study MM-010: Patients were enrolled from 22 September 2003 at 50 sites in Australia (6 sites), Europe (41 sites), and Israel (3 sites). Data cut-off for the final study report was 03 August 2005 when the study was unmasked.

Conduct of the study

At the time of the interim analysis, the pre-determined stopping criteria for superiority in the primary efficacy endpoint TTP were met. Patients still on study were given the option of receiving open-label treatment with lenalidomide/dexamethasone.

Baseline data

Patient population baseline demographic and disease characteristics are displayed in Tables 4 and 5.

Table 4: Studies MM-009 and MM-010 - Demographic and disease characteristics

Characteristics	Study MM-009		Study MM-010	
	Len/Dex N=177	Pbo/Dex N=176	Len/Dex N=176	Pbo/Dex N=175
Age (years)				
Mean	63.3	62.5	62.2	62.9
Min, Max	36.0, 86.0	37.0, 85.0	10.12	8.80
Sex				
Male	106 (59.9%)	104 (59.1%)	104 (59.1%)	103 (58.9%)
Female	71 (40.1%)	72 (40.9%)	72 (40.9%)	72 (41.1%)
Race/Ethnicity	141 (79.7%)			
White	25 (14.1%)	148 (84.1%)	172 (97.7%)	175 (100.0%)
Black	3 (1.7%)	17 (9.7%)	2 (1.1%)	0 (0%)
Hispanic	5 (2.8%)	5 (2.8%)	0 (0%)	0 (0%)
Asian/Pacific Islander	3 (1.7%)	2 (1.1%)	1 (0.6%)	0 (0%)
Other		4 (2.3%)	1 (0.6%)	0 (0%)
Time From First Pathologic Diagnosis (years)				
n	177	176	176	175
Mean	3.6	3.9	4.2	4.8
SD	2.44	2.74	2.86	3.55
Median	3.1	3.1	3.4	4.0
Min, Max	0.5, 14.7	0.0, 19.7	0.4, 15.7	0.3, 26.6
Baseline Multiple Myeloma Stage				
I	6 (3.4%)	5 (2.8%)	11 (6.3%)	8 (4.6%)
II	56 (31.6%)	55 (31.3%)	50 (28.4%)	57 (32.6%)
III	114 (64.4%)	116 (65.9%)	115 (65.3%)	110 (62.9%)
Missing	1 (0.6%)	0 (0%)	0 (0%)	0 (0%)
Multiple Myeloma Progression Manifested				
Rising M-paraprotein levels	168 (94.9%)	167 (94.9%)	162 (92.0%)	156 (89.1%)
Worsening lytic bone disease	31 (17.5%)	38 (21.6%)	43 (24.4%)	56 (32.0%)
Worsening extramedullary plasmacytoma disease	7 (4.0%)	7 (4.0%)	5 (2.8%)	7 (4.0%)
ECOG Performance Status				
0	74 (41.8%)	85 (48.3%)	78 (44.3%)	65 (37.1%)
1	83 (46.9%)	83 (47.2%)	72 (40.9%)	79 (45.1%)
2	14 (7.9%)	6 (3.4%)	23 (13.1%)	27 (15.4%)
3	0 (0%)	0 (0%)	0 (0%)	1 (0.6%)
Missing	6 (3.4%)	2 (1.1%)	3 (1.7%)	3 (1.7%)
Lytic Bone Lesions	121 (68.4%)	133 (75.6%)		
Present	55 (31.1%)	43 (24.4%)	136 (77.3%)	140 (80.0%)
Absent	1 (0.6%)	0 (0%)	40 (22.7%)	35 (20.0%)
Missing			0 (0%)	0 (0%)
Bone Marrow Aspirate/Biopsy Cellularity				
Normal	72 (40.7%)	75 (42.6%)	107 (60.8%)	102 (58.3%)
Hyperplasia	67 (37.9%)	65 (36.9%)	41 (23.3%)	41 (23.4%)
Hypoplasia	30 (16/9%)	28 (15.9%)	26 (14.8%)	28 (16.0%)
Missing	4 (2.3%)	6 (3.4%)	2 (1.1%)	3 (1.7%)
Percent Plasma Cells				
n	172	170	172	169
Mean	34.2	31.8	36.2	31.1
SD	27.75	26.67	28.39	26.37
Median	27.5	25.0	30.0	22.0
Min, Max	0.0, 95.0	0.0, 100.0	0.0, 100.0	0.0, 100.0
Baseline β_2-microglobulin				
$\leq$ 2.5 mg/l	52 (29.4%)	51 (29.0%)	51 (29.0%)	48 (27.4%)
> 2.5 mg/l	125 (70.6%)	125 (71.0%)	125 (71.0%)	127 (72.6%)

Table 5: Studies MM-009 and MM-010 - Prior anti-myeloma therapy

Type of Therapy	Study MM-009		Study MM-010	
	Len/Dex N=177	Pbo/Dex N=176	Len/Dex N=176	Pbo/Dex N=175
Previously Treated with HDT/SCT				
Yes	109 (61.6%)	108 (61.4%)	97 (55.1%)	95 (54.3%)
No	68 (38.4%)	68 (38.6%)	79 (44.9%)	80 (45.7%)
No. of Prior Anti-myeloma Therapies				
1	68 (38.4%)	67 (38.1%)	56 (31.8%)	57 (32.6%)
2 or 3	109 (61.6%)	109 (61.9%)	120 (68.2%)	118 (67.4%)
Prior Anti-myeloma Regimens or SCT				
1	35 (19.8%)	40 (22.7%)	30 (17.0%)	33 (18.9%)
2	72 (40.7%)	69 (39.2%)	66 (37.5%)	65 (37.1%)
3	52 (29.4%)	45 (25.6%)	62 (35.2%)	61 (34.9%)
> 3	18 (10.2%)	22 (12.5%)	18 (10.2%)	16 (9.1%)
Prior SCT				
0	69 (39.0%)	70 (39.8%)	77 (43.8%)	81 (46.3%)
1	100 (56.5%)	95 (54.0%)	71 (40.3%)	61 (34.9%)
2	8 (4.5%)	11 (6.3%)	28 (15.9%)	33 (18.9%)
Prior Radiotherapy				
Yes	56 (31.6%)	64 (36.4%)	57 (32.4%)	51 (29.1%)
No	121 (68.4%)	112 (63.6%)	119 (67.6%)	124 (70.9%)
Prior Thalidomide Therapy				
Yes	74 (41.8%)	80 (45.5%)	53 (30.1%)	67 (38.3%)
No	103 (58.2%)	96 (54.5%)	123 (69.9%)	108 (61.7%)
Prior Dexamethasone Therapy				
Yes	143 (80.8%)	124 (70.5%)	116 (65.9%)	120 (68.6%)
No	34 (19.2%)	52 (29.5%)	60 (34.1%)	55 (31.4%)
Prior Bortezomib Therapy				
Yes	19 (10.7%)	20 (11.4%)	8 (4.5%)	7 (4.0%)
No	158 (89.3%)	156 (88.6%)	168 (95.5%)	168 (96.0%)
Prior Melphalan Therapy				
Yes	59 (33.3%)	54 (30.7%)	99 (56.3%)	91 (52.0%)
No	118 (66.7%)	122 (69.3%)	77 (43.8%)	84 (48.0%)
Prior Doxorubicin Therapy				
Yes	97 (54.8%)	90 (51.1%)	98 (55.7%)	99 (56.6%)
No	80 (45.2%)	86 (48.9%)	78 (44.3%)	76 (43.4%)

SCT, stem cell transplantation

Numbers analysed

Study MM-009: 353 patients were randomised (177 in the lenalidomide/dexamethasone group and 176 in the placebo/dexamethasone group).

Study MM-010: 351 patients were randomised (176 in the lenalidomide/group and 175 in the placebo/dexamethasone group).

Outcomes and estimation

Primary endpoint analyses

Table 6 presents the results for both studies for the primary endpoint of the primary analysis (interim analysis with the following cut-off dates: 15 July 2004 for Study MM-009 and 15 September 2004 for Study MM-010).

Table 6: Studies MM-009 and MM-010 - Summary of time-to-progression by protocol definition (primary analysis)

		Study MM-009		Study MM-010	
		Len/Dex	**Pbo/Dex**	**Len/Dex**	**Pbo/Dex**
TTP	N	170	171	176	175
Progressed	n (%)	44 (25.9)	98 (57.3)	39 (22.2)	99 (56.6)
Censored	n (%)	126 (74.1)	73 (42.7)	137 (77.8)	76 (43.4)
	Median (weeks)	41.1	20.1	NE	20.1
	[95% CI]	[30.3, NE]	[16.7, 24.1]	[36.1, NE]	[20.0, 22.1]
Hazard Ratio [95% CI]		3.073 [2.149, 4.395]		3.246 [2.239, 4.708]	
Log-rank test *P*-value		< 0.001		< 0.001	

NE, not estimable

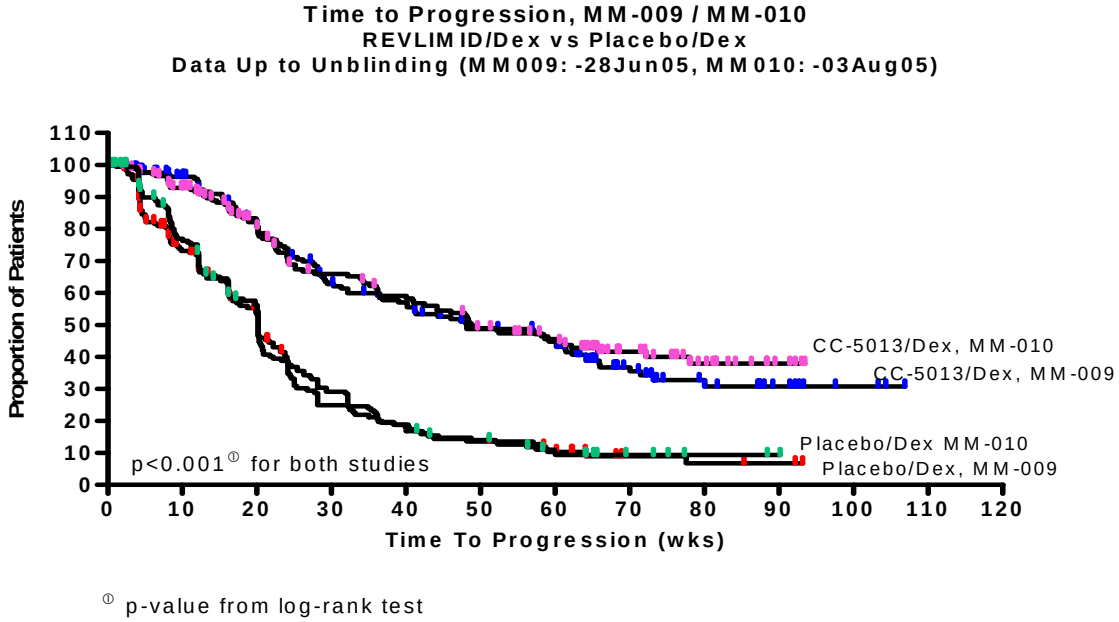
Data of 12 patients of one centre of Study MM-009 were sequestered at the time of the primary analysis

Table 7 and Figure 1 present the results for both studies for the primary endpoint of secondary analysis (final analysis when both studies were unmasked, cut-off dates: 28 June 2005 for Study MM-009 and 03 August 2005 for Study MM-010).

Table 7: Studies MM-009 and MM-010 - Summary of time-to-progression by protocol definition (secondary analysis)

			Study MM-009		Study MM-010	
		Statistic	**Len/Dex**	**Pbo/Dex**	**Len/Dex**	**Pbo/Dex**
TTP		N	177	176	176	175
Progressed		n (%)	92 (52.0)	132 (75.0)	82 (46.6)	142 (81.1)
Censored		n (%)	85 (48.0)	44 (25.0)	94 (53.4)	33 (18.9)
Overall TTP (weeks)		Median	48.1	20.1	48.7	20.1
		[95% CI]	[36.9, 1.4]	[16.7, 23.1]	[40.9, 72.1]	[18.1, 20.7]
Hazard Ratio [95% CI]			2.822 [2.146, 3.701]		2.850 [2.159, 3.762]	
Log-rank Test p-Value			< 0.001		< 0.001	

Figure 1: Studies MM-009 and MM-010 - Kaplan-Meier Estimate of time-to-progression (secondary analysis)



① p-value from log-rank test

Further results in this report refer to the secondary analysis performed when both studies were unmasked (cut-off dates: 28 June 2005 for Study MM-009 and 03 August 2005 for Study MM-010) with more mature data.

Secondary endpoint analyses
Tables 8 and 9 present the results for both studies for the secondary endpoint analyses.

Table 8: Studies MM-009 and MM-010 - Summary of response rates based on best response assessments (secondary analysis)

	Study MM-009		Study MM-010	
	Len/Dex N=177	Pbo/Dex N=176	Len/Dex N=176	Pbo/Dex N=175
Response				
Complete Response (CR)	25 (14.1%)	1 (0.6%)	28 (15.9%)	6 (3.4%)
Remission Response (RR)	52 (29.4%)	16 (9.1%)	46 (26.1%)	16 (9.1%)
Partial Response (PR)	31 (17.5%)	18 (10.2%)	32 (18.2%)	20 (11.4%)
Stable Disease (SD)	54 (30.5%)	102 (58.0%)	53 (30.1%)	97 (55.4%)
Progressive Disease (PD)	5 (2.8%)	25 (14.2%)	3 (1.7%)	25 (14.3%)
Not Evaluable (NE)	10 (5.6%)	14 (8.0%)	14 (8.0%)	11 (6.3%)
p-value	< 0.001		< 0.001	
Dichotomised Response				
CR, RR or PR	108 (61.0%)	35 (19.9%)	106 (60.2%)	42 (24.0%)
SD, PD or NE	69 (39.0%)	141 (80.1%)	70 (39.8%)	133 (76.0%)
p-value	< 0.001		< 0.001	
Odds Ratio	6.31		4.80	
[95% CI]	[3.91, 10.17]		[3.03, 7.59]	

Table 9: Studies MM-009 and MM-010 - Summary of time-to-first worsening of ECOG performance status (secondary analysis)

		Study MM-009		Study MM-010	
	Statistic	Len/Dex N=177	Pbo/Dex N=176	Len/Dex N=176	Pbo/Dex N=175
Time to First Worsening	N				
Worsened	n (%)	171	174	173	172
Censored	n (%)	88 (51.5)	101 (58.0)	111 (64.2)	97 (56.4)
		83 (48.5)	73 (42.0)	62 (35.8)	75 (43.6)
Overall Time to First	Median	36.3	12.1	10.1	12.3
Worsening (wk)	[95% CI]	[16.1, NE]	[8.3, 16.4]	[8.1, 16.1]	[10.1, 24.1]
	Mean	30.6	15.2	20.6	17.9
	SD	31.11	17.25	23.36	18.13
	Min, Max	0.0, 104.3	0.0, 80.9	0.0, 93.0	0.0, 88.4
Hazard Ratio [95% CI]		1.448 [1.083, 1.937]		0.858 [0.653, 1.128]	
Log-rank Test p-Value		0.012		0.271	

NE, not estimable

Overall survival for Study MM-009 showed a significant survival advantage for lenalidomide/dexamethasone relative to placebo/dexamethasone. Thirty-seven (20.9%) of the 177 lenalidomide/dexamethasone-treated patients, compared with 62 (35.2%) of the 176 of the placebo/dexamethasone-treated patients, had died. Based on Kaplan-Meier estimates, median OS was 93.4 weeks for the placebo/dexamethasone-treated patients.

No significant difference in OS had been observed between the lenalidomide/dexamethasone- and the placebo/dexamethasone-treated patients in Study MM-010 (47 and 59 deaths, respectively).

- Analysis performed across trials (pooled analyses and meta-analysis)

Table 10 displays the results of analysis of a pooled data of both studies (MM-009 and MM-010). The median treatment duration was 28.1 weeks (min: 0.1, max: 110.7).

Table 10: Studies MM-009 and MM-010 - Summary of efficacy results analyses (secondary analysis on pooled data)

	Len/Dex (N=353)	Pbo/Dex (N=351)	Hazard/odds ratio, 95% CI, p-value
Median TTP [weeks]	48.3	20.1	0.35 [0.29, 0.43]
[95% CI]	[41.1, 60.1]	[19.9, 20.7]	p<0.001 [b]
OR [n, %]	214 (60.6)	77 (21.9)	0.18 [0.13, 0.25], p < 0.001
CR [n, %]	53 (15.0)	7 (2.0)	0.12 [0.05,0.26], p < 0.001
RR+PR [n, %]	161 (45.6)	70 (19.9)	0.30 [0.21, 0.42], p < 0.001
Median PFS [weeks]	47.3	20.1	0.38 [0.32, 0.46]
[95% CI]	[36.9, 58.4]	[18.1, 20.3]	p < 0.001

The overall survival in the pooled studies at one year was 82% in patients treated with lenalidomide/dexamethasone versus 75% in patients treated with placebo/dexamethasone, after the start of treatment, with a median follow-up duration of 98.0 weeks (min: 0.3, max: 163.3). Despite the fact that 170 out of the 351 patients randomised to placebo/dexamethasone received treatment with lenalidomide/dexamethasone after the studies were unmasked, the pooled analysis of OS demonstrated a statistically significant survival advantage for lenalidomide/dexamethasone relative to placebo/dexamethasone (hazard/odds ratio: 0.75, 95% CI: [0.59, 0.95], p = 0.015).

Results of TTP/PFS on the subgroup of patients showing primary resistance on thalidomide confirmed the effectiveness of lenalidomide/dexamethasone treatment compared to placebo/dexamethasone. Even in the subset of patients previously treated thalidomide who developed progressive disease or who had progressive disease as best response, TTP and PFS times were significantly prolonged in the lenalidomide/dexamethasone group.

- Clinical studies in special populations

No studies in special populations e.g. in children, in the elderly and in patients with hepatic impairment was performed.

Subgroup analyses by gender, age, baseline serum β_2-microglobulin level, prior therapy, and number of prior anti-myeloma regimens were conducted separately for Studies MM-009 and MM-010. In both studies, differences in TTP, favouring lenalidomide/dexamethasone, were observed irrespective of gender, age, baseline serum β_2-microglobulin level, prior therapy with high-dose chemotherapy or SCT or not, and the number of prior anti-myeloma regimens.

Study CC-5013-CHF-00-001 is a single-centre, placebo-controlled, double-blind, dose-escalation study of lenalidomide in patients with New York Heart Association (NYHA) Class II-IV heart failure. Three dose levels were planned: 5, 10 and 25 mg/day. Up to 21 patients were to be enrolled, depending upon the level at which toxicity was observed. At each dose level, seven patients were to be randomised to either study drug or placebo at a ratio of 5:2. The primary endpoint was safety, as assessed by adverse events, ECG, and serum chemistry, haematology and urinalysis. The secondary endpoints were the change in left ventricular end-diastolic diameter after 12 weeks, as measured by 2-dimensional echocardiogram and the change in left ventricular ejection fraction after 12 weeks, as measured by multiple gated acquisition (MUGA) study.

The study was terminated by recommendation of the data safety monitoring board (DSMB) after completion of the 5 and 10 mg dose-groups with 14 of the planned 21 patients enrolled. The DSMB recommended that no additional patients be enrolled into the study due to the absence of obvious benefit and the inability to rule out the potential safety concern of hyperthyroidism.

- Discussion on clinical efficacy

The recommended starting dose of lenalidomide is 25 mg orally once daily on Days 1-21 of repeated 28-day cycles. The recommended dose of dexamethasone is 40 mg orally once daily on Days 1-4, 9-12, and 17-20 of each 28-day cycle for the first 4 cycles of therapy and then 40 mg once daily on days 1-4 every 28 days. Dosing is continued or modified based upon clinical and laboratory findings.

Lenalidomide treatment must not be started if the absolute neutrophil count (ANC) is < 1.0 x 10^9 /l, and/or platelet count is < 75 x 10^9 /l or, dependent on bone marrow infiltration by plasma cells, platelet count is < 30 x 10^9 /l.

The outcome of the primary analysis, the sensitivity analyses and the secondary analysis is consistent and convincing in showing that lenalidomide is effective in combination with dexamethasone for the treatment of relapsed or refractory multiple myeloma. Analysis of OS for Study MM-009 showed a significant survival advantage for lenalidomide/dexamethasone relative to placebo/dexamethasone.

Subgroup analyses were conducted separately for Studies MM-009 and MM-010. Significant differences in TTP, favouring lenalidomide/dexamethasone, were observed irrespective of gender, age, baseline serum β_2-microglobulin level, prior therapy with high-dose chemotherapy or SCT or not, and the number of prior anti-myeloma regimens.

Lenalidomide/dexamethasone compared with placebo/dexamethasone was effective in terms of TTP and PFS in the subgroup of patients showing primary resistance on thalidomide, and even in the subset of patients previously treated with thalidomide who developed progressive disease while treated or who had progressive disease as best response.

In the pivotal trials, only a minority of patients had received bortezomib (54/704 in both pivotal studies). In the patients who had received prior bortezomib therapy, TTP was significantly longer among the lenalidomide/dexamethasone-treated patients than among the placebo/dexamethasone-treated patients. Prior treatment with bortezomib has no obvious effect on the efficacy of lenalidomide/dexamethasone combination.

At the time of submission, there was no experience in children and adolescents. Therefore, lenalidomide should not be used in the paediatric age group (0-17 years) even if the multiple myeloma does not affect this age group.

Clinical safety

The assessment of the safety profile of lenalidomide in the claimed indication was focused on the two main studies (MM-009 and MM-010) evaluating efficacy and the safety of lenalidomide plus oral pulse high-dose of dexamethasone versus oral pulse high-dose of dexamethasone alone in patients with relapsed or refractory multiple myeloma.

Safety evaluations included physical examination, vital signs, haematology and biochemical testing, thyroid function tests (TSH, tri-iodothyronine [T_3], and thyroxine [T_4] were determined at screening/baseline, every 8 weeks starting with Cycle 2, and at treatment discontinuation), 12-lead ECG, appropriate imaging studies and a pregnancy test for female participants.

- Patient exposure

The pooled safety database as of 31 December 2005 includes 703 patients (353 in the lenalidomide/dexamethasone group and 350 in the placebo/dexamethasone group). Table 11 details the patient exposure for the 2 pivotal studies.

Table 11: Studies MM-009 and MM-010 - Duration of treatment

	Len/Dex N=353		Pbo/Dex N=350	
Treatment Phase Duration (Weeks)				
	n	**%**	**n**	**%**
<1 week	1	0.3	2	0.6
1 to < 4 weeks	14	4.0	14	4.0
4 to < 8 weeks	14	4.0	38	10.9
8 to < 12 weeks	27	7.6	42	12.0
12 to < 16 weeks	15	4.2	28	8.0
16 to < 20 weeks	18	5.1	31	8.9
20 to < 24 weeks	16	4.5	23	6.6
24 to < 28 weeks	19	5.4	38	10.9
28 to < 32 weeks	19	5.4	27	7.7
32 to < 36 weeks	10	2.8	12	3.4
36 to < 40 weeks	11	3.1	15	4.3
40 to < 44 weeks	12	3.4	13	3.7
44 to < 48 weeks	8	2.3	8	2.3
48 to < 52 weeks	6	1.7	4	1.1
≥52 weeks	163	46.2	55	15.7
Duration of Exposure (Weeks)				
n	353		350	
Mean	53.9		29.7	
SD	38.76		26.41	
Median	44.0		23.1	
Min, Max	0.1, 161.7		0.3, 124.0	

- Adverse events

Table 12 presents pooled results of all adverse events that were reported by the patients or observed by the investigators and recorded in the case report form (CRF) for Studies MM-009 and MM-010. The severity of adverse events and laboratory abnormalities was graded according to National Cancer Institute (NCI) Common Toxicity Criteria (CTC) (Version 2.0).

Table 12: Studies MM-009 and MM-010 - Adverse events reported in at least 10% of patients in either treatment group

MedDRA System Organ Class/ Preferred Term	Len/Dex (N=353) Grade 1-4 n (%)	Len/Dex (N=353) Grade 3/4 n (%)	Pbo/Dex (N=350) Grade 1-4 n (%)	Pbo/Dex (N=350) Grade 3-4 n (%)
Blood and Lymphatic System Disorders				
Neutropenia	152 (43.1)	125 (35.4)	23 (6.6)	12 (3.4)
Anaemia NOS	119 (33.7)	38 (10.8)	83 (23.7)	21 (6.0)
Thrombocytopenia	80 (22.7)	46 (13.0)	37 (10.6)	22 (6.3)
Eye Disorders				
Vision Blurred	60 (17.0)	1 (0.3)	40 (11.4)	1 (0.3)
Gastrointestinal Disorders				
Constipation	149 (42.2)	8 (2.3)	77 (21.7)	2 (0.6)
Diarrhoea NOS	137 (38.8)	11 (3.1)	98 (28.0)	4 (1.1)
Nausea	92 (26.1)	7 (2.0)	76 (21.7)	2 (0.6)
Dyspepsia	59 (16.7)	1 (0.3)	51 (14.6)	2 (0.6)
Vomiting NOS	42 (11.9)	4 (1.1)	32 (9.1)	4 (1.1)
Abdominal Pain NOS	37 (10.5)	5 (1.4)	22 (6.3)	1 (0.3)
General Disorders and Administration Site Conditions				
Fatigue	161 (45.6)	25 (6.5)	129 (37.4)	17 (4.9)
Asthenia	103 (29.2)	17 (4.8)	86 (24.9)	18 (5.1)
Pyrexia	100 (28.3)	5 (1.4)	67 (19.4)	12 (3.4)
Oedema Peripheral	95 (26.9)	6 (1.7)	65 (18.8)	4 (1.1)
Oedema NOS	37 (10.5)	3 (0.8)	33 (9.4)	2 (0.6)
Infections and Infestations				
Upper Respiratory Tract Infection NOS	87 (24.6)	5 (1.4)	55 (15.7)	2 (0.6)
Pneumonia NOS	49 (13.9)	32 (9.1)	30 (8.6)	19 (5.4)
Investigations				
Weight Decreased	68 (19.3)	3 (0.9)	53 (15.1)	1 (0.3)
Metabolism and Nutrition Disorders				
Hyperglycaemia NOS	57 (16.1)	27 (7.6)	50 (14.3)	27 (7.7)
Anorexia	57 (16.1)	2 (0.6)	36 (10.3)	3 (0.9)
Hypokalaemia	52 (14.7)	20 (5.7)	21 (6.0)	5 (1.4)
Musculoskeletal and Connective Tissue Disorders				
Muscle Cramp	121 (34.3)	3 (0.9)	76 (21.7)	1 (0.3)
Back Pain	91 (25.8)	6 (1.7)	67 (19.1)	6 (1.7)
Arthralgia	63 (17.8)	2 (0.6)	63 (18.0)	7 (2.0)
Muscle Weakness NOS	56 (16.0)	20 (5.7)	56 (16.0)	11 (3.1)
Bone Pain	51 (14.4)	8 (2.3)	40 (11.4)	5 (1.4)
Pain in Limb	41 (11.6)	1 (0.3)	33 (9.4)	5 (1.4)
Myalgia	37 (10.5)	4 (1.1)	38 (10.9)	2 (0.6)
Nervous System Disorders				
Headache	94 (26.6)	3 (0.8)	85 (24.3)	1 (0.3)
Dizziness	83 (23.5)	7 (2.0)	59 (16.9)	3 (0.9)
Tremor	75 (21.2)	2 (0.6)	26 (7.4)	4 (1.1)
Dysgeusia	54 (15.3)	0 (0)	34 (9.7)	0 (0)
Paraesthesia	51 (14.4)	1 (0.3)	47 (13.4)	0 (0)
Hypoesthesia	37 (10.5)	1 (0.3)	26 (7.4)	0 (0)
Psychiatric Disorders				
Insomnia	129 (36.5)	4 (1.1)	133 (38.0)	1 (0.3)
Depression	45 (12.7)	10 (2.8)	37 (10.6)	6 (1.7)
Respiratory, Thoracic, and Mediastinal Disorders				
Cough	90 (25.5)	2 (0.6)	86 (24.6)	1 (0.3)
Dyspnoea NOS	85 (24.1)	10 (2.8)	60 (17.1)	10 (2.9)
Nasopharyngitis	65 (18.4)	2 (0.6)	31 (8.9)	0 (0)
Pharyngitis	53 (15.0)	0 (0)	34 (9.7)	0 (0)
Bronchitis NOS	41 (11.6)	2 (0.6))	30 (8.6)	5 (1.4)
Skin and Subcutaneous Tissue Disorders				
Rash NOS	76 (21.5)	2 (0.6)	35 (10.0)	0 (0)
Vascular Disorders - none ≥ 10% frequency				

NOS, not otherwise specified

Anaemia, neutropenia, thrombocytopenia, constipation, pneumonia, weight decreased, hypokalaemia, hypocalcaemia, tremor, rash, and deep vein thrombosis (DVT) were reported significantly more frequently in the lenalidomide/dexamethasone group than in the placebo/dexamethasone group.

Neutropenia and thrombocytopenia were the primary reasons for dose reductions in the lenalidomide/dexamethasone group.

Cardiac adverse events are more frequently reported in lenalidomide/dexamethasone arm (18.1%) than in placebo/dexamethasone arm (11.1%), particularly atrial fibrillation (4.2% including 3.1% serious) with lenalidomide/dexamethasone and 1.1% with placebo/dexamethasone (0.6% were serious). Of the 69 lenalidomide-treated patients experiencing cardiac adverse events (including irregular hear rate, cardiac murmur, decreased ejection fraction and abnormal ECG, Q wave, ST-T segment and prolonged QT), 56 were found to have had either an underlying conditions or were taking concomitant medications (i.e., beta blocker, Ca channel blocker, anti-arrhythmic, etc.).

Peripheral neuropathy: only few cases suggesting a peripheral neuropathy are reported in those 2 studies, and their incidence is comparable between lenalidomide/dexamethasone and placebo/dexamethasone groups (about 5 to 8% of drug-related peripheral sensory neuropathies/paraesthesia).

Vascular disorders: there was a significant increased risk for developing thromboembolic adverse events (deep vein thrombosis, pulmonary embolism) in lenalidomide/dexamethasone-treated patients compared with placebo/dexamethasone–treated patients (9.1% versus 4.3% and 4.0% versus 0.9%, respectively). Risk factors have been identified: 1) concomitant erythropoietin treatment (EPO), 2) thrombosis past medical history, 3) older age and 4) lower baseline plasma cell. Moreover, all of the cases of thrombosis presented rising M-paraprotein at baseline.

- Serious adverse event/deaths/other significant events

Table 13 displays all serious adverse events observed in Studies MM-009 and MM-010.

Table 13: Studies MM-009 and MM-010 - Number (%) of patients with serious adverse events reported in at least 1% of patients

MedDRA System Organ Class/ Preferred Term	Len/Dex (N=353)		Pbo/Dex (N=350)	
	n	%	n	%
Patients with at least one serious adverse event	202	57.2	163	46.6
Infections and Infestations	81	22.9	59	16.9
Pneumonia NOS	34	9.6	22	6.3
Respiratory Tract Infection NOS	4	1.1	7	2.0
Sepsis NOS	4	1.1	5	1.4
Upper Respiratory Tract Infection NOS	4	1.1	1	0.3
Urinary Tract Infection NOS	4	1.1	1	0.3
Vascular Disorders	40	11.3	20	5.7
Deep Vein Thrombosis	25	7.1	11	3.1
Hypotension NOS	2	0.6	4	1.1
General Disorders and Administration Site Conditions	29	8.2	20	5.7
Pyrexia	12	3.4	13	3.7
Metabolism and Nutrition Disorders	25	7.1	24	6.9
Dehydration	7	2.0	6	1.7
Hyperglycaemia NOS	5	1.4	6	1.7
Hypercalcaemia	1	0.3	6	1.7
Respiratory, Thoracic, and Mediastinal Disorders	25	7.1	22	6.3
Pulmonary Embolism	13	3.7	3	0.9
Nervous System Disorders	24	6.8	19	5.4
Cerebrovascular Accident	7	2.0	3	0.9
Gastrointestinal Disorders	22	6.2	19	5.4
Diarrhoea NOS	6	1.7	2	0.6
Abdominal Pain NOS	4	1.1	1	0.3
Renal and Urinary Disorders	17	4.8	17	4.9
Renal Failure NOS	6	1.7	9	2.6
Renal Failure Acute	5	1.4	4	1.1
Cardiac Disorders	27	7.6	12	3.4
Atrial Fibrillation	11	3.1	2	0.6
Cardiac Failure Congestive	5	1.4	0	0
Pulmonary Oedema NOS	1	0.3	4	1.1
Blood and Lymphatic System Disorders	22	6.2	9	2.6
Febrile Neutropenia	6	1.7	0	0
Thrombocytopenia	5	1.4	5	1.4
Anaemia NOS	5	1.4	2	0.6
Neutropenia	5	1.4	1	0.3
Musculoskeletal and Connective Tissue Disorders	18	5.1	12	3.4
Bone Pain	4	1.1	0	0

NOS, not otherwise specified

As of 31 December 2005, 107 (30.3%) deaths had been reported among the 353 lenalidomide/dexamethasone-treated patients and 142 (40.5%) deaths had been reported among the 351 placebo/dexamethasone-treated patients. The primary cause of death in both treatment groups was disease progression (70/107 in lenalidomide/dexamethasone group and 101/142 in placebo/dexamethasone group).

Of the 107 deaths in the lenalidomide/dexamethasone group, 24 were suspected by the investigators to be related to the study medication. Of the 142 deaths in the placebo/dexamethasone group, 24 were suspected by the investigator to be related to the study medication.

- Laboratory findings

No clinically significant changes were noted for vital signs measurements or clinical laboratory values. This included thyroid-stimulating hormone, the thyroid function test.

No clinically important effects of lenalidomide/dexamethasone relative to placebo/dexamethasone were observed on ECG. A small number of patients in each treatment group (2 in the lenalidomide/dexamethasone group and 3 in the placebo/dexamethasone group) had a worsening (e.g., a normal finding at baseline and a clinically significant finding at the end of treatment) in their

ECG from baseline to the end of treatment; the follow-up ECG abnormalities were generally not suspected by the investigators to be related to treatment with the study medications.

Little variation in body weight was observed in either treatment group during the study. Mean body weight decreased in both treatment groups during the first 6 cycles of therapy and then tended to increase after Cycle 6.

- Safety in special populations

No formal studies have been conducted to assess the effects of age, gender, race or hepatic impairment on the pharmacokinetics of lenalidomide. However, the available clinical data do not indicate that adjustments in the dose of lenalidomide are needed for safety-related reasons in these subpopulations.

Except for Grade 3/4 anaemia, which was reported significantly more frequently in females (17.5%; 25/143) than in males (6.2%; 13/210) and DVT was reported significantly more frequently in males (11.0%; 23/210) than in females (3.5%; 53/143) in the lenalidomide/dexamethasone group. No other significant differences between genders were observed.

- Safety related to drug-drug interactions and other interactions

Safety related to drug-drug interactions was investigated in 2 interaction studies and assessed by adverse events, clinical laboratory findings, physical examinations, vital signs, and ECG.

Warfarin interaction study

There were no clinically meaningful changes in clinical laboratory findings, physical examinations, vital signs, or ECG. The adverse events were all mild in severity and evenly divided between lenalidomide and placebo. The most frequent adverse events were dermatological and were also evenly reported by lenalidomide (35% of subjects) and placebo (41% of subjects), beginning after the warfarin dose on Day 4. As expected during warfarin therapy, elevations in prothrombin time (PT) and international normalised ratio (INR) were observed during the study. However, based on a comparison of the PT and INR values that were observed during co-administration of placebo and warfarin and those that were observed during co-administration of lenalidomide and warfarin, co-administration of lenalidomide had no effect on PT or INR. Moreover, the results of this study show no pharmacokinetic or pharmacodynamic interactions between lenalidomide and warfarin; therefore, lenalidomide and warfarin may be co-administered.

Digoxin interaction study

Only 3 mild adverse events (headache, sinus headache, somnolence) were reported by 3 (16%) of the 19 subjects dosed in this study. The adverse events occurred in the placebo group prior to digoxin administration. There were neither serious adverse events reported, nor subjects were discontinued from the study due to adverse events and all adverse events resolved without therapy.

- Discontinuation due to adverse events

In the pivotal studies, treatment discontinuations rates for adverse events were comparable between the 2 treatment groups, Table 14 provides details on the main adverse events leading to treatment discontinuation.

Table 14: Studies MM-009 and MM-010 - Number (%) of patients with adverse events leading to discontinuation reported in at least 1% of patients

MedDRA System Organ Class/ Preferred Term	Len/Dex (N=353)		Pbo/Dex (N=350)	
	n	%	n	%
Patients with at least one adverse event leading to discontinuation of study drug	83	24.9	63	18.0
Blood and Lymphatic System Disorders	23	6.5	10	2.9
Neutropenia	10	2.8	2	0.6
Thrombocytopenia	6	1.7	3	0.9
Anaemia NOS	2	0.6	6	1.7
General Disorders and Administration Site Conditions	9	2.5	6	1.7
Asthenia	3	0.8	4	1.1
Infections and Infestations	7	2.0	10	2.9
Pneumonia NOS	3	0.8	4	1.1
Nervous System Disorders	15	4.2	9	2.6
Cerebrovascular Accident	4	1.1	1	0.3
Neuropathy NOS	4	1.1	0	0
Psychiatric Disorders	8	2.3	8	2.3
Confusional State	4	1.1	1	0.3
Respiratory, Thoracic, and Mediastinal Disorders	11	3.1	6	1.7
Pulmonary Embolism	9	2.5	1	0.3
Skin and Subcutaneous Tissue Disorders	5	1.4	0	0
Rash NOS	3	0.8	0	0

- Post-marketing experience

Lenalidomide was approved in the United States on 27 December 2005 and data were available on 5075 medically confirmed adverse reactions have been reported in 2275 patients during the period covered by a Periodic Safety Update Report. Of these, 2087 were serious. There were 194 reports with fatal outcome. Of these, the primary cause of death was the progression of the disease in 33% of reports, unknown or unreported in 36% of the reports. For the other reports, the primary causes of death for the other reports were sepsis (n = 11), pneumonia (n = 7), leukaemia (n = 6), cardiac failure congestive (n = 4), renal failure (n = 4) and myocardial infarction (n = 4).

- Discussion on clinical safety

Treatment with Revlimid must be initiated and monitored under the supervision of physicians experienced in the management of multiple myeloma (MM).

Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. The teratogenic effect of lenalidomide cannot be ruled out. For lenalidomide no clinical data on exposed pregnancies are available. Studies in animals have shown embryofoetal toxicity. Therefore, lenalidomide is contraindicated during pregnancy. Women of childbearing potential should use effective method of contraception. If pregnancy occurs in a woman treated with lenalidomide, treatment must be stopped and the patient should be referred to a physician specialised or experienced in teratology for evaluation and advice. For male patients taking lenalidomide, there is no clinical data available on the presence of lenalidomide in human semen. Therefore male patients taking lenalidomide should use condoms if their partner is of childbearing potential and has no contraception.

The potential teratogenicity induced by lenalidomide in human is still the main safety issue that needs further investigation. The combination with dexamethasone is also problematic since this drug possesses liver enzyme induction capacities, which might affect the pregnancy protection with anti-contraceptive pills. No interaction study has been performed with oral contraceptives. Dexamethasone is known to be a weak to moderate inducer of CYP3A4 and is likely to also affect other enzymes as well as transporters. It may not be excluded that the efficacy of oral contraceptives may be reduced during treatment. Effective measures to avoid pregnancy must be taken (as detailed in the SPC).

Pooled safety data, including adverse events, laboratory findings, vital signs, and electrocardiogram (ECG) data, from two pivotal, Phase III, multicentre, randomised, double-blind, placebo-controlled studies of lenalidomide/dexamethasone combination therapy versus placebo/dexamethasone therapy, were provided as evidence of the safety of the lenalidomide/dexamethasone combination for relapsed and refractory multiple myeloma (Study MM-009 and Study MM-010); 353 patients were treated with the lenalidomide/dexamethasone combination and 350 patients were treated with placebo/dexamethasone in these studies.

The most serious adverse reactions were:
- Venous thromboembolism (deep vein thrombosis, pulmonary embolism) (as stated in the SPC,
- Grade 4 neutropenia (as stated in the SPC).

The most frequently observed drug-related adverse events which occurred significantly more frequently in the lenalidomide/dexamethasone group compared to the placebo/dexamethasone group were: neutropenia (39.4%), fatigue (27.2%), asthenia (17.6%), constipation (23.5%), muscle cramp (20.1%), thrombocytopenia (18.4%), anaemia (17.0%), diarrhoea (14.2%) and rash (10.2%).

Among the SAE reported at a higher than 1% frequency serious DVT, pulmonary embolism and cardiac disorders including serious atrial fibrillation occurred more commonly in the lenalidomide exposed population. DVT occurred in 25 versus 11 patients and pulmonary embolism occurred in 11 versus 3 patients treated with lenalidomide/dexamethasone vs. placebo/dexamethasone. A dose-dependent thrombotic risk for lenalidomide has been observed. Other factors associated with thrombotic risk included the concomitant use of erythropoietin/growth factors, past medical history, older age, and lower baseline plasma cell.

No formal studies have been conducted to assess the effects of age, gender, race or hepatic impairment on the pharmacokinetics of lenalidomide. However, the available clinical data do not indicate that adjustments in the dose of lenalidomide are needed for safety-related reasons in these subpopulations. Since multiple myeloma affects an elderly population it is of interest to further investigate age in relation to side effects of lenalidomide.

It is not known whether lenalidomide is excreted in human milk. Therefore breast-feeding should be discontinued during therapy with lenalidomide.

There is no specific experience in the management of lenalidomide overdose in multiple myeloma patients, although in dose-ranging studies some patients were exposed to up to 50 mg. The dose limiting toxicity in these studies was essentially haematological. In the event of overdose, supportive care is advised.

1.5 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 MAA submitted a risk management plan, which included a risk minimisation plan.

Table 15: Summary of the risk management plan

Safety issue	Proposed Pharmacovigilance activities	Proposed risk minimisation activities
Neutropenia and thrombocytopenia	• Routine Pharmacovigilance • Additional information from ongoing clinical trials • Post-Authorisation Safety Study (PASS) to monitor incidence in "real world" situation	• Section 4.2 of SPC Dose reduction advice for neutropenia and thrombocytopenia • Section 4.4 of SPC Warning of neutropenia and thrombocytopenia and advise for weekly blood tests for first eight weeks and then monthly • Listed as ADR in Section 4.8 of SPC • Direct Healthcare Professional Communication prior to launch • Health Care Professional Kit • Patient Brochure
Infection	• Routine Pharmacovigilance • Additional information from ongoing clinical trials • Post-Authorisation Safety Study to monitor incidence in "real world" situation • Data from US Rev Assist Programme whereby accurate post-market exposure data is available	• Section 4.2 of SPC Dose reduction advice for neutropenia • Section 4.4 of SPC Warning of neutropenia and advise for weekly blood tests for first eight weeks and then monthly • Listed as ADR in Section 4.8 of SPC • Direct Healthcare Professional Communication prior to launch • Health Care Professional Kit • Patient Brochure
Bleeding events	• Routine Pharmacovigilance • Additional information from ongoing clinical trials • Post-Authorisation Safety Study to monitor incidence in "real world" situation • Data from US Rev Assist Programme whereby accurate post-market exposure data is available	• Section 4.2 of SPC Dose reduction advice for thrombocytopenia • Section 4.4 of SPC Warning of thrombocytopenia and advise for weekly blood tests for first eight weeks and then monthly • Listed as ADR in Section 4.8 of SPC • Direct Healthcare Professional Communication prior to launch • Health Care Professional Kit • Patient Brochure
Thrombosis/ thromboembolism	• Routine Pharmacovigilance • Additional information from ongoing clinical trials • Post-Authorisation Safety Study to monitor incidence in "real world" situation • Data from US Rev Assist Programme whereby accurate post-market exposure data is available • A randomised comparative clinical trial in patients treated for MM to provide recommendations for preventing thromboembolism events in lenalidomide treated patients	• Section 4.4 of SPC Warning • Section 4.5 Interactions –advise against use with other thrombogenic agents • Listed as ADR in Section 4.8 of SPC Listed as ADR in Section 4.8 of SPC • Direct Healthcare Professional Communication prior to launch • Health Care Professional (HCP) Kit • Patient Brochure

Safety issue	Proposed Pharmacovigilance activities	Proposed risk minimisation activities
Foetal exposure	• Routine Pharmacovigilance • Enhanced reporting of pregnancies to Celgene by HCP-Pregnancy report form included in all HCP Kits • Follow-up of all pregnancies until at least the pregnancy outcome and in case of congenital malformation until final diagnosis • Root cause analysis of failed Pregnancy Prevention Programme (PPP) as part of standard follow up • Expedited reporting of all Pregnancies • Review of Pregnancies in PSUR • Post-Authorisation Safety Study to monitor implementation of PPP • Additional monitoring of implementation of PPP on a country specific basis in accordance with local legal framework i.e. monitoring of patient card completion, monitoring by external agency and surveys • A PK study planned to evaluate transfer of lenalidomide in semen in order to assess the risk for the foetus after paternal exposure	• Section 4.3 of SPC: Contraindicated in pregnancy and in women of childbearing potential unless all of the conditions of the Pregnancy Prevention Programme (PPP) are met • Section 4.6 Pregnancy and Lactation • Section 4.4 Warnings: Pregnancy warning. Details of Pregnancy Prevention Programme including: o Criteria for women of non childbearing potential o Counselling o Contraception o Pregnancy testing o Precautions for men o Additional precautions o Reference to the company providing Educational materials • A warning statement to the Carton: "Lenalidomide may be harmful to an unborn child" • Pregnancy Prevention Programme o Educational Programme • Direct Healthcare Professional Communication prior to launch • Educational Health Care Professional Kit to include HCP booklet, Treatment Algorithm, Pregnancy Reporting Form, Patient Card and Checklists • Patient Brochure o Therapy Management • Criteria for determining women of childbearing potential (WCBP), effective contraceptive measures for WCBP, regular pregnancy testing for WCBP • Advise provided on SPC, outlined in Direct Healthcare Professional Communication and detailed in Educational Materials o System to ensure all appropriate measures have been completed • Patient card to document childbearing status, counselling and pregnancy testing
Peripheral Neuropathy	• Routine Pharmacovigilance • Additional information from ongoing clinical trials specifically to monitor effects of long-term exposure, and patients previously exposed to thalidomide • Post-Authorisation Safety Study to monitor incidence in "real world"	• Section 4.4 of SPC Warning • Listed as ADR in Section 4.8 of SPC • Direct Healthcare Professional Communication prior to launch • Health Care Professional Kit • Patient Brochure

Safety issue	Proposed Pharmacovigilance activities	Proposed risk minimisation activities
	situation • Data from US Rev Assist Programme whereby accurate post-market exposure data is available	
Cardiac failure Cardiac arrhythmias QT prolongation	• Routine Pharmacovigilance • Additional information from ongoing clinical trials • Post-Authorisation Safety Study to monitor incidence in "real world" situation • Data from US Rev Assist Programme whereby accurate post-market exposure data is available • QTc study healthy volunteers	• Listed as ADR in Section 4.8 of SPC
Hypersensitivity	• Routine Pharmacovigilance • Additional information from ongoing clinical trials • Post-Authorisation Safety Study to monitor incidence in "real world" situation • Data from US Rev Assist Programme whereby accurate post-market exposure data is available	• Section 4.3 of SPC: Contraindicated if hypersensitivity to the active substance or to any of the excipients
Rash	• Routine Pharmacovigilance • Additional information from ongoing clinical trials • Post-Authorisation Safety Study to monitor incidence in "real world" situation • Data from US Rev Assist Programme whereby accurate post-market exposure data is available	• Listed as ADR in Section 4.8 of SPC
Endocrine disorders	• Routine Pharmacovigilance • Additional information from ongoing clinical trials • Post-Authorisation Safety Study to monitor incidence in "real world" situation • Data from US Rev Assist Programme whereby accurate post-market exposure data is available	• Section 4.4 of SPC: Warning of hypothyroidism and advise to monitor • Thyroid disorders listed as ADR in Section 4.8 of SPC
Use in renal failure	• Routine Pharmacovigilance • Post-Authorisation Safety Study to monitor incidence in "real world" situation	• Section 4.2: Dose adjustments at start of therapy for patients with renal failure based on Study CC 5013-PK-001 • Section 4.4 of SPC: Warning for monitoring of renal function in patients with renal impairment
Off-label use	• Routine Pharmacovigilance	

Safety issue	Proposed Pharmacovigilance activities	Proposed risk minimisation activities
	• Data from US Rev Assist Programme whereby accurate post-market exposure data is available • Continuous follow-up of use and lenalidomide indications after approval in the EU (to be adapted on a country basis)	

The Risk Management Plan is adequate to address the issue of teratogenicity and other safety concerns.

Special caution is recommended regarding other adverse events, less frequently reported but compatible with a pharmacovigilance signal:

- Cardiac function: changes in ECG, atrial fibrillation, bradycardia
- Metabolic disorders: hypokalaemia
- Endocrine disorders: hypothyroidism
- Visual disorders: blurred vision

Given morbidity and/or mortality usually associated with those adverse events, a preventive treatment should be considered at least for patients with identified risk factors even if there is no specific data proving efficacy for prevention of lenalidomide induced-thrombotic events. Since efficacy of aspirin on thrombotic events prophylaxis has not been proved, preventive treatment should be heparin or oral anticoagulant. Consequently, the Applicant is asked to perform a randomized, comparative, clinical study assessing the efficacy of prophylactic treatment for thrombotic events in patients with multiple myeloma receiving lenalidomide.

Recommended dose adjustments during treatment and restart of treatment
Dose adjustments, as summarised below, are recommended to manage Grade 3 or 4 neutropenia or thrombocytopenia, or other grade 3 or 4 toxicity judged to be related to lenalidomide.

- *Dose reduction steps*

Starting dose	25 mg
Dose level 1	15 mg
Dose level 2	10 mg
Dose level 3	5 mg

- *Platelet counts*

Thrombocytopenia

When platelets	Recommended Course
First fall to < 30 x 10^9/l Return to ≥ 30 x 10^9/l	Interrupt lenalidomide treatment Resume lenalidomide at Dose Level 1
For each subsequent drop below 30 x 10^9/l Return to ≥ 30 x 10^9/l	Interrupt lenalidomide treatment Resume lenalidomide at next lower dose level (Dose Level 2 or 3) once daily. Do not dose below 5 mg once daily.

- *Absolute Neutrophil counts (ANC)*

Neutropenia

When neutrophils	Recommended Course
First fall to < 0.5 x 10^9/l Return to ≥ 0.5 x 10^9/l when neutropenia is the only observed toxicity	Interrupt lenalidomide treatment Resume lenalidomide at Starting Dose once daily
Return to ≥ 0.5 x 10^9/l when dose-dependent haematological toxicities other than neutropenia are observed	Resume lenalidomide at Dose Level 1 once daily
For each subsequent drop below < 0.5 x 10^9/l Return to ≥ 0.5 x 10^9/l	Interrupt lenalidomide treatment Resume lenalidomide at next lower dose level (Dose Level 2 or 3) once daily. Do not dose below 5 mg once daily.

In case of neutropenia, the physician should consider the use of growth factors in patient management.

Pregnancy warning

Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. If lenalidomide is taken during pregnancy, a teratogenic effect of lenalidomide cannot be ruled out.

The conditions of the Pregnancy Prevention Programme must be fulfilled for all patients unless there is reliable evidence that the patient does not have childbearing potential.

Criteria for women of non-childbearing potential

A female patient or a female partner of a male patient is considered to have childbearing potential unless she meets at least one of the following criteria:

- Age ≥ 50 years and naturally amenorrhoeic for ≥ 1 year*
- Premature ovarian failure confirmed by a specialist gynaecologist
- Previous bilateral salpingo-oophorectomy, or hysterectomy
- XY genotype, Turner syndrome, uterine agenesis.

Counselling

For women of childbearing potential, lenalidomide is contraindicated unless all of the following are met:

- She understands the potential teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, 4 weeks before starting treatment, throughout the entire duration of treatment, and 4 weeks after the end of treatment
- Even if a woman of childbearing potential has amenorrhea she must follow all the advice on effective contraception
- She should be capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to rapidly consult if there is a risk of pregnancy
- She understands the need to commence the treatment as soon as lenalidomide is dispensed following a negative pregnancy test
- She understands the need and accepts to undergo pregnancy testing every 4 weeks except in case of confirmed tubal sterilisation
- She acknowledges that she understands the hazards and necessary precautions associated with the use of lenalidomide.

* Amenorrhoea following cancer therapy does not rule out childbearing potential

For male patients taking lenalidomide, there is no clinical data available on the presence of lenalidomide in human semen. Male patients taking lenalidomide must meet the following conditions:

- Understand the potential teratogenic risk if engaged in sexual activity with a woman of childbearing potential
- Understand the need for the use of a condom if engaged in sexual activity with a woman of childbearing potential.

The prescriber must ensure that for women of childbearing potential:

- The patient complies with the conditions for Pregnancy Prevention Programme, including confirmation that she has an adequate level of understanding
- The patient has acknowledged the aforementioned conditions.

Contraception

Women of childbearing potential must use one effective method of contraception for 4 weeks before therapy, during therapy, and until 4 weeks after lenalidomide therapy and even in case of dose interruption unless the patient commits to absolute and continuous abstinence confirmed on a monthly basis. If not established on effective contraception, the patient must be referred to an appropriately trained health care professional for contraceptive advice in order that contraception can be initiated.

The following can be considered to be examples of suitable methods of contraception:

- Implant
- Levonorgestrel-releasing intrauterine system (IUS)
- Medroxyprogesterone acetate depot
- Tubal sterilisation
- Sexual intercourse with a vasectomised male partner only; vasectomy must be confirmed by two negative semen analyses
- Ovulation inhibitory progesterone-only pills (i.e., desogestrel)

Because of the increased risk of venous thromboembolism in patients with multiple myeloma taking lenalidomide and dexamethasone, combined oral contraceptive pills are not recommended (as stated in the SPC, section 4.5). If a patient is currently using combined oral contraception the patient should switch to one of the effective method listed above. The risk of venous thromboembolism continues for 4−6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone (as stated in the SPC, section 4.5).

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in patients with neutropenia.

Copper-releasing intrauterine devices are generally not recommended due to the potential risks of infection at the time of insertion and menstrual blood loss which may compromise patients with neutropenia or thrombocytopenia.

Pregnancy testing

According to local practice, medically supervised pregnancy tests with a minimum sensitivity of 25 IU/ml must be performed for women of childbearing potential as outlined below.

Prior to starting treatment

A medically supervised pregnancy test should be performed during the consultation, when lenalidomide is prescribed, or in the 3 days prior to the visit to the prescriber once the patient had been using effective contraception for at least 4 weeks. The test should ensure the patient is not pregnant when she starts treatment with lenalidomide.

Follow-up and end of treatment

A medically supervised pregnancy test should be repeated every 4 weeks, including 4 weeks after the end of treatment, except in the case of confirmed tubal sterilisation. These pregnancy tests should be performed on the day of the prescribing visit or in the 3 days prior to the visit to the prescriber.

Men
It is not known whether lenalidomide is present in semen. Therefore all male patients should use condoms throughout treatment duration, during dose interruption and for 1 week after cessation of treatment if their partner is of childbearing potential and has no contraception.

Additional precautions
Ideally, pregnancy testing, issuing a prescription and dispensing should occur on the same day. Dispensing of lenalidomide should occur within a maximum of 7 days of the prescription.

Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to their pharmacist at the end of treatment.

Patients should not donate blood or semen during therapy or for 1 week following discontinuation of lenalidomide.

Educational materials
In order to assist patients in avoiding foetal exposure to lenalidomide, the Marketing Authorisation Holder will provide educational material to health care professionals to reinforce the warnings about the potential teratogenicity of lenalidomide, to provide advice on contraception before therapy is started, and to provide guidance on the need for pregnancy testing. Full patient information about the potential teratogenic risk and the strict pregnancy prevention measures as specified in the Pregnancy Prevention Programme should be given by the physician to women of childbearing potential and, as appropriate, to male patients.

Other special warnings and precautions for use
Venous thromboembolism
The combination of lenalidomide with dexamethasone is associated with an increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients with multiple myeloma (as stated in the SPC, sections 4.5 and 4.8). Concomitant administration of erythropoietic agents or previous history of DVT may also increase thrombotic risk in these patients. Therefore, erythropoietic agents, or other agents that may increase the risk of thrombosis, such as hormone replacement therapy, should be used with caution in multiple myeloma patients receiving lenalidomide with dexamethasone. Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, arm or leg swelling. Prophylactic antithrombotic medicines, such as low molecular weight heparins or warfarin, should be recommended, especially in patients with additional thrombotic risk factors. The decision to take antithrombotic prophylactic measures should be made after careful assessment of an individual patient's underlying risk factors.

Neutropenia and thrombocytopenia
The combination of lenalidomide with dexamethasone in multiple myeloma patients is associated with a higher incidence of grade 4 neutropenia (5.1% in lenalidomide/dexamethasone-treated patients compared with 0.6% in placebo/dexamethasone-treated patients; as stated in the SPC, section 4.8). Grade 4 febrile neutropenia episodes were observed infrequently (0.6% in lenalidomide/dexamethasone-treated patients compared to 0.0% in placebo/dexamethasone treated patients; as stated in the SPC, section 4.8). Patients should be advised to promptly report febrile episodes. A dose reduction may be required (as stated in the SPC, section 4.2). In case of neutropenia, the physician should consider the use of growth factors in patient management.

The combination of lenalidomide with dexamethasone in multiple myeloma patients is associated with a higher incidence of grade 3 and grade 4 thrombocytopenia (9.9% and 1.4%, respectively, in lenalidomide/dexamethasone-treated patients compared to 2.3% and 0.0% in placebo/dexamethasone-treated patients; as stated in the SPC, section 4.8). Patients and physicians are

advised to be observant for signs and symptoms of bleeding, including petechiae and epistaxes. A dose reduction may be required (as stated in the SPC, section 4.2).

A complete blood cell count, including white blood cell count with differential count, platelet count, haemoglobin, and haematocrit should be performed at baseline, every week for the first 8 weeks of lenalidomide treatment and monthly thereafter to monitor for cytopenias.

The major dose limiting toxicities of lenalidomide include neutropenia and thrombocytopenia. Therefore, co-administration of lenalidomide with other myelosuppressive agents should be undertaken with caution.

Renal impairment
Lenalidomide is substantially excreted by the kidney. Therefore care should be taken in dose selection and monitoring of renal function is advised in patients with renal impairment (as stated in the SPC, section 4.2).

Thyroid function
Cases of hypothyroidism have been reported and monitoring of thyroid function should be considered.

Peripheral neuropathy
Lenalidomide is structurally related to thalidomide, which is known to induce severe peripheral neuropathy. At this time, the neurotoxic potential of lenalidomide associated with long-term use cannot be ruled out.

Lactose intolerance
Revlimid capsules contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Unused capsules
Patients should be advised never to give this medicinal product to another person and to return any unused capsules to their pharmacist at the end of the treatment.

Erythropoietic agents or other agents that may increase the risk of thrombosis, such as hormone replacement therapy, should be used with caution in multiple myeloma patients receiving lenalidomide with dexamethasone (as stated in the SPC, sections 4.4 and 4.8).

The CHMP, having considered the data submitted in the application is of the opinion that the following risk minimisation activities as detailed above in this document are necessary for the safe and effective use of the medicinal product (see benefit-risk assessment).

1.6 Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of this medicinal product is considered satisfactory when used with the conditions defined in the SPC. The documentation provided for the active substance lenalidomide is comprehensive and adequately detailed. The pharmaceutical development is adequate for this oral formulation and took into consideration properties such as particle size and polymorphism and the stability of the active substance. The excipients are those typically used for capsule formulations. Similarly, the packaging material is well documented and no incompatibility has been noticed. The validation of the manufacturing process ensures consistency and reproducibility of the finished medicinal product. The finished medicinal product has been satisfactorily controlled and stability studies conducted under ICH conditions showed that the medicinal product is stable throughout the proposed shelf life.

At the time of the CHMP opinion, there were some outstanding quality issues with no impact on the benefit/risk. The applicant undertook to provide the necessary information as follow-up measures

within an agreed timeframe and to submit variations if required following the evaluation of this additional information.

Non-clinical pharmacology and toxicology

Lenalidomide has been developed based on the structure and pharmacology of thalidomide. In vitro data suggest that lenalidomide is much more potent. Lenalidomide was 10-1000 times more potent than thalidomide in various in vitro pharmacology studies of immunomodulatory, anti-proliferative, and pro-erythropoietic activities. The molecular target of lenalidomide remains unknown. In vivo, lenalidomide was shown to delay tumour growth and prolong survival in a mouse xenograft model with human lymphoma cells. Lenalidomide showed effect on solid tumour cell growth in two mouse models. Inhibition of angiogenesis was demonstrated in an in vivo model in the rat.

The primary toxicities observed after repeated oral administrations of lenalidomide were associated with the haematopoietic lympho-reticular systems and the kidneys, generally reversible after a 4- to 7-week recovery period. Rats appeared to be more sensitive to the effects on the kidneys, while cynomolgus monkeys were more sensitive to the effects on the haematopoietic systems. The NOAEL for rats in the chronic 26-week toxicity study was set at < 75 mg/kg/day. Based on AUC comparison, this dose was approximately 25-fold greater than the human daily exposure. In repeated-dose toxicity studies in monkeys, NOAEL is less than 1 mg/kg; this dose was equivalent to the human daily exposure (safety margin: 0.95 to 1).

Lenalidomide showed no evidence for genotoxicity. Further *in vitro* characterisation of the genotoxicity of the active substance including impurities will be performed as a follow-up measure.
Carcinogenicity studies with lenalidomide have not been conducted.

A fertility and early embryonic development study in male and female rats, with administration of lenalidomide up to 500 mg/kg/day, produced no parental toxicity and no adverse effects on fertility or early embryonic development.

Developmental toxicity studies were conducted in rats and rabbits. In rats, lenalidomide was not teratogenic at oral doses of up to 500 mg/kg/day. Nevertheless, rat species is not considered as a relevant model for thalidomide analogues.

In the rabbit, lenalidomide exhibited foetal toxicity with increased post-implantation loss, decreased foetal weight, and also an increased frequency of foetal alterations (absence of the intermediate lobe of the lung and displaced kidneys) and variations.

Based on the structural and pharmacological similarity to thalidomide and the foetal alterations observed in the rabbit study, lenalidomide should be contraindicated during pregnancy, and precautions should be taken for women of childbearing potential (see risk management plan). The embryotoxic and teratogenic potential of lenalidomide will be further characterised as a post-approval commitment, in the most relevant and sensitive species (follow-up measure).

Efficacy

The lenalidomide mechanism of action includes anti-neoplastic, anti-angiogenic, pro-erythropoietic, and immunomodulatory properties. Specifically, lenalidomide inhibits proliferation of certain haematopoietic tumour cells (including MM plasma tumour cells and those with deletions of chromosome 5), enhances T cell- and Natural Killer (NK) cell-mediated immunity and increases the number of NK T cells, inhibits angiogenesis by blocking the migration and adhesion of endothelial cells and the formation of microvessels, augments foetal haemoglobin production by CD34+ haematopoietic stem cells, and inhibits production of pro-inflammatory cytokines (e.g., TNF-α and IL-6) by monocytes.

Clinical trials

The efficacy and safety of lenalidomide were evaluated in two Phase III, multicentre, randomised, double-blind, placebo-controlled, parallel-group controlled studies (MM-009 and MM-010) of lenalidomide plus dexamethasone therapy versus dexamethasone alone in previously treated patients with multiple myeloma. Out of 353 patients in the MM-009 and MM-010 studies who received lenalidomide/dexamethasone, 45.6% were aged 65 or over. Of the 704 patients evaluated in the MM-009 and MM-010 studies, 44.6% were aged 65 or over.

In both studies, patients in the lenalidomide/dexamethasone 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. Patients in the placebo/dexamethasone group took 1 placebo capsule on Days 1 to 28 of each 28-day cycle. Patients 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. The dose of dexamethasone was reduced to 40 mg orally once daily on Days 1 to 4 of each 28-day cycle after the first 4 cycles of therapy. In both studies, treatment was to continue until disease progression. In both studies, dose adjustments were allowed based on clinical and laboratory finding.

The primary efficacy endpoint in both studies was time to progression (TTP). In total, 353 patients were evaluated in the MM-009 study; 177 in the lenalidomide/dexamethasone group and 176 in the placebo/dexamethasone group and, in total, 351 patients were evaluated in the MM-010 study; 176 in the lenalidomide/dexamethasone group and 175 in the placebo/dexamethasone group.

In both studies, the baseline demographic and disease-related characteristics were comparable between the lenalidomide/dexamethasone and placebo/dexamethasone groups. Both patient populations presented a median age of 63 years, with a comparable male to female ratio. The ECOG performance status was comparable between both groups, as was the number and type of prior therapies.

Pre-planned interim analyses of both studies showed that lenalidomide/dexamethasone was statistically significantly superior ($p < 0.00001$) to dexamethasone alone for the primary efficacy endpoint, TTP. Complete response (CR) and overall response (OR) rates in the lenalidomide/dexamethasone arm were also significantly higher than the dexamethasone/placebo arm in both studies. Results of these analyses subsequently led to an unblinding in both studies, in order to allow patients in the placebo/dexamethasone group to receive treatment with the lenalidomide/dexamethasone combination.

In a pooled follow-up analysis of studies MM-009 and MM-010 (N = 704), the median TTP was 48.3 weeks (95% CI: 41.1, 60.1) in patients treated with lenalidomide/dexamethasone (n = 353) versus 20.1 weeks (95% CI: 19.9, 20.7) in patients treated with placebo/dexamethasone (n = 351). The median time of progression free survival (PFS) was 47.3 weeks (95% CI: 36.9, 58.4) in patients treated with lenalidomide/dexamethasone versus 20.1 weeks (95% CI: 18.1, 20.3) in patients treated with placebo/dexamethasone. The median duration of treatment was 28.1 weeks (min: 0.1, max: 110.7). Complete response (CR), partial response (PR) and overall response (OR) rates in the lenalidomide/dexamethasone arm were significantly higher than in the dexamethasone/placebo arm in both studies. The overall survival (OS) in the pooled studies at one year after the start of treatment was 82% in patients treated with lenalidomide/dexamethasone versus 75% in patients treated with placebo/dexamethasone, with a median follow-up duration of 98.0 weeks (min: 0.3, max: 163.3). Despite the fact that 170 out of the 351 patients randomised to placebo/dexamethasone received treatment with lenalidomide/dexamethasone after the studies were unblinded, the pooled analysis of OS demonstrated a statistically significant survival advantage for lenalidomide/dexamethasone relative to placebo/dexamethasone (hazard ratio = 0.75, 95% CI = [0.59, 0.95], p = 0.015). Table 1 summarises key efficacy results of the pooled follow-up analyses of studies MM-009 and MM-010.

Safety

In two Phase III, placebo-controlled studies, 353 patients with multiple myeloma were exposed to the lenalidomide/dexamethasone combination and 351 to the placebo/dexamethasone combination. The median duration of exposure to study treatment was significantly longer (44.0 weeks) in the

lenalidomide/dexamethasone group as compared to placebo/dexamethasone (23.1 weeks). The difference was accounted for by a lower rate of discontinuation from study treatment due to lower progression of disease in patients exposed to lenalidomide/dexamethasone (39.7%) than in placebo/dexamethasone patients (70.4%).

Three hundred twenty-five (92%) of the patients in the lenalidomide/dexamethasone group experienced at least one adverse reaction compared to 288 (82%) in the placebo/dexamethasone group.

The most serious adverse reactions were:

- Venous thromboembolism (deep vein thrombosis, pulmonary embolism) (as stated in the SPC, section 4.4)
- Grade 4 neutropenia (as stated in the SPC, section 4.4).

The most frequently observed adverse reactions which occurred significantly more frequently in the lenalidomide/dexamethasone group compared to the placebo/dexamethasone group were neutropenia (39.4%), fatigue (27.2%), asthenia (17.6%), constipation (23.5%), muscle cramp (20.1%), thrombocytopenia (18.4%), anaemia (17.0%), diarrhoea (14.2%) and rash (10.2%).

The adverse reactions observed in patients treated with lenalidomide/dexamethasone are listed below by system organ class and frequency. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000), very rare (< 1/10,000 including isolated reports). In the majority of cases, there was no significant difference in the incidence of specific adverse events between the two treatment arms.

The potential teratogenicity induced by lenalidomide in human needs further investigation. The combination with dexamethasone is also problematic since this drug possesses liver enzyme induction capacities, which might affect the pregnancy protection with anti-contraceptive pills. The Risk Management Plan adequately addresses teratogenicity together with other safety concerns.

Risk-benefit assessment

As compared to dexamethasone only, lenalidomide and dexamethasone induced a prolongation of median TTP by roughly at least 28 weeks, a result that has been observed in both pivotal studies. Such an increased TTP might correspond to delayed symptoms and complications and appear as a clinical benefit as long as survival data do not contradict these results. Supplementary analyses do confirm that the benefit observed for TTP is also obtained with PFS.

Toxicities observed in studies of lenalidomide alone were low; the incidence of peripheral neuropathy was significantly lower than those noted in trials using thalidomide. Leucopenia and thrombocytopenia were significant Grade 3 or 4 toxicities observed; however, it was manageable with dose reduction.

In contrast with high-dose dexamethasone, deep vein thrombosis has emerged as an important toxicity. An increase in deep vein thrombosis is indeed reported with lenalidomide, especially in patients who received erythropoietin. These data confirmed that the use of erythropoietin promotes deep vein thrombosis in patients with multiple myeloma (in Study MM-009 7.5% in the placebo/dexamethasone arm associated with erythropoietin versus 1% without erythropoietin) but also showed that lenalidomide increases this risk in these patients (overall 22.6% in the lenalidomide/dexamethasone arm associated with erythropoietin versus 4.8% without erythropoietin).

Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. If lenalidomide is taken during pregnancy, a teratogenic effect of lenalidomide cannot be ruled out.

The conditions of the Pregnancy Prevention Programme must be fulfilled for all patients unless there is reliable evidence that the patient does not have childbearing potential

Revlimid is contraindicated in case of:

- Women who are pregnant.
- Women of childbearing potential unless all of the conditions of the Pregnancy Prevention Programme are met (as stated in the SPC, sections 4.4 and 4.6).
- Hypersensitivity to the active substance or to any of the excipients.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns.
- plus the following additional risk minimisation activities were required:
    - A Direct Healthcare Professional Communication to be sent at the time of launch with the following core message:
        - Approved indication of the medicinal product
        - Conditions of the Pregnancy Prevention Programme together with the definition of women of childbearing potential and effective contraceptive method, requirements of pregnancy testing and instruction for men patients
        - Awareness of risk of venous thromboembolism, myelosuppression, hypothyroidism and management in case of renal failure
        - Controlled distribution system implemented at a national level
    - Educational material for patient and healthcare professional includes:
        - A Healthcare Professional kit including information on lenalidomide licensed indication, description and management of neutropenia and thrombocytopenia, thrombotic risk, use in hepatic and renal impairment, description of the Pregnancy Prevention Programme with the definition of women of childbearing potential and effective contraceptive method, requirements of pregnancy testing and reporting (pregnancy reporting form)
        - A patient brochure with information on multiple myeloma, treatment instruction, pregnancy prevention programme and side effects
        - A patient card which includes documentation of childbearing potential status, acknowledgement that counselling has taken place, contraceptive method used for women of childbearing potential, pregnancy test date and result, confirmation that there is no risk of pregnancy.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Revlimid in the treatment of multiple myeloma in combination with dexamethasone in patients who have received at least one prior therapy was favourable and therefore recommended the granting of the marketing authorisation.