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IMPORTANT SAFETY INFORMATION

Revlimid® (lenalidomide)

New Preclinical Safety Information on Teratogenicity from Ongoing Primate Embryofoetal Development Study: EU SmPC Update

Celgene, in agreement with the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMEA) and national competent authorities, including the Irish Medicines Board (IMB) wishes to inform you about the following new safety information relating to Revlimid® (lenalidomide):

- Preliminary results of an ongoing study show that lenalidomide is teratogenic in animals and is expected to be teratogenic in humans
- The SmPC for Revlimid has been updated, to reflect these preclinical results and clearly state that a teratogenic effect of lenalidomide in humans is expected
- Healthcare Professionals are advised to carefully follow the pregnancy prevention measures as specified in the **Pregnancy Prevention Programme** and the SmPC to avoid any foetal exposure to lenalidomide during pregnancy

Revlimid® (lenalidomide) is authorised in combination with dexamethasone for the treatment of multiple myeloma patients who have received at least one previous therapy.

Important preliminary results have been obtained from an ongoing primate embryofoetal development study conducted with lenalidomide (final results expected March 2009). Malformations (short limbs, bent digits, wrist and/or tail, supernumerary or absent digits) were observed in the offspring of female monkeys who received lenalidomide during pregnancy. Thalidomide produced similar types of malformations in the same study.

Although preliminary, these results show that lenalidomide is teratogenic in animals, in a similar way as thalidomide, and is expected to be teratogenic in humans.

Prior to these findings, the EU Summary of Product Characteristics (SmPC) stated that Revlimid was a potential human teratogen and the Revlimid Pregnancy Prevention Programme was put in place to provide guidance to healthcare professionals and patients to avoid foetal exposure.

In light of these findings, the SmPC for Revlimid has been updated, to reflect these preclinical results and clearly state that a teratogenic effect of lenalidomide in humans is expected. Educational Healthcare Professional's Kit and Educational brochures for patients will also be revised to reflect this latest information. Please find enclosed a copy of the updated SmPC with tracked changes. Please note that these changes have been approved by the Committee for

Medicinal Products for Human Use (CHMP), but have not yet been authorised by the European Commission (EC).

Celgene wishes to remind Healthcare Professionals that they must carefully follow the strict pregnancy prevention measures as specified in the **Pregnancy Prevention Programme** and the SmPC to avoid any foetal exposure to lenalidomide during pregnancy.

Women of childbearing potential as defined in the SmPC should use one effective method of contraception for at least 4 weeks before therapy, during therapy, during dose interruptions and 4 weeks after therapy has finished. A pregnancy test must be performed before initiating treatment, monthly thereafter and 4 weeks after the end of treatment.

Full details, including measures to be taken by male patient to avoid foetal exposure, are also provided in the Educational Healthcare professional's kit.

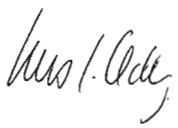
The practical implementation of the Risk Management Programme in Ireland will not be affected.

Any suspected adverse reactions associated with use of Revlimid should be notified to the company and/or the IMB, in the usual way.

Should you have any questions related to the use of Revlimid, please contact Celgene (details below).

The content of this communication has been approved by the CHMP and the IMB.

Yours sincerely,



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ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Revlimid 5 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 5 mg of lenalidomide.

Excipient:
Each capsule contains 147 mg of anhydrous lactose.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

White capsules marked "REV 5 mg".

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

Administration
Revlimid capsules should be taken at about the same time each day. The capsules should not be broken or chewed. The capsules should be swallowed whole, preferably with water, either with or without food. If less than 12 hours has elapsed since missing a dose, the patient can take the dose. If more than 12 hours has elapsed since missing a dose at the normal time, the patient should not take the dose, but take the next dose at the normal time on the following day.

Recommended dose
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 (see section 4.4).

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

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	Interrupt lenalidomide treatment
Return to ≥ 30 x 10^9/l	Resume lenalidomide at Dose Level 1
For each subsequent drop below 30 x 10^9/l	Interrupt lenalidomide treatment
Return to ≥ 30 x 10^9/l	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	Interrupt lenalidomide treatment
Return to ≥ 0.5 x 10^9/l when neutropenia is the only observed toxicity	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	Interrupt lenalidomide treatment
Return to ≥ 0.5 x 10^9/l	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.

Paediatric patients
There is no experience in children and adolescents. Therefore, lenalidomide should not be used in the paediatric age group (0-17 years).

Elderly patients
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 (see section 5.1). 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.

Use in patients with impaired 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 (CLcr)	Dose Adjustment
Mild renal impairment (CLcr ≥ 50 ml/min)	25 mg once daily (Full Dose)
Moderate renal impairment (30 ≤ CLcr < 50 ml/min)	10 mg once daily*
Severe renal impairment (CLcr < 30 ml/min, not requiring dialysis)	15 mg every other day
End Stage Renal Disease (ESRD) (CLcr < 30 ml/min, requiring dialysis)	15 mg, 3 times a week following each dialysis

* The dose may be escalated to 15 mg once daily after 2 cycles if patient is not responding to treatment and is tolerating the treatment.

Use in patients with impaired hepatic function
Lenalidomide has not formally been studied in patients with impaired hepatic function and there are no specifie dose recommendations.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Pregnancy warning
Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. Lenalidomide induced in monkeys malformations similar to those described with thalidomide (see sections 4.6 and 5.3). If lenalidomide is taken during pregnancy, a teratogenic effect of lenalidomide in humans is expected.

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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.

*Amenorrhoea following cancer therapy does not rule out childbearing potential.

Counselling
For women of childbearing potential, lenalidomide is contraindicated unless all of the following are met:
- She understands the expected teratogenic risk to the unborn child

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- 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.

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 expected 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.

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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 (see also 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 (see 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 mIU/ml must be performed for women of childbearing potential as outlined below. This requirement includes women of childbearing potential who practice absolute and continuous abstinence. Ideally, pregnancy testing, issuing a prescription and dispensing should occur on the same

day. Dispensing of lenalidomide to women of childbearing potential should occur within 7 days of the prescription.

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
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 expected 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 expected 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.

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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 (see 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. A haemoglobin concentration above 13 g/dl should lead to discontinuation of erythropoietic agents. 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; see 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; see section 4.8). Patients should be advised to promptly report febrile episodes. A dose reduction may be required (see 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; see 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 (see 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 (see 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.

Tumour Lysis Syndrome
Because lenalidomide has anti-neoplastic activity the complications of tumour lysis syndrome may occur. The patients at risk of tumour lysis syndrome are those with high tumour burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

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.

4.5 Interaction with other medicinal products and other forms of interaction

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 (see sections 4.4 and 4.8).

Oral contraceptives
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 (see sections 4.4 and 4.6).

Results from human *in vitro* metabolism studies indicate that lenalidomide is not metabolised by cytochrome P450 enzymes suggesting that administration of lenalidomide with drugs that inhibit cytochrome P450 enzymes is not likely to result in metabolic drug interactions in man. *In vitro* studies indicate that lenalidomide has no inhibitory effect on CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A.

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.

4.6 Pregnancy and lactation

Pregnancy (see also sections 4.3 and 4.4)
Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects.

Lenalidomide induced in monkeys, malformations similar to those described with thalidomide (see section 5.3). Therefore, a teratogenic effect of lenalidomide is expected and lenalidomide is contraindicated during pregnancy (see section 4.3).

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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. If pregnancy occurs in a partner of a male patient taking lenalidomide, it is recommended to refer the female partner 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.

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

4.7 Effects on ability to drive and use machines

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.

4.8 Undesirable effects

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%).

325 (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) (see section 4.4)
- Grade 4 neutropenia (see 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. Only those adverse reactions marked with * occurred significantly more frequently in the lenalidomide/dexamethasone arm compared to the placebo/dexamethasone arm.

Adverse Drug Reactions (ADRs) observed in patients treated with lenalidomide/dexamethasone:

Investigations
Uncommon: Prolonged prothrombin time, prolonged activated partial thromboplastin time, increased International Normalised Ratio, increased blood alkaline phosphatase, increased blood lactate dehydrogenase, increased C-Reactive Protein, *Cytomegalovirus* antibody positive

Cardiac disorders
Common: Atrial fibrillation, palpitations
Uncommon: Congestive cardiac failure, pulmonary oedema, heart valve insufficiency, atrial flutter, arrhythmia, ventricular trigeminy, bradycardia, tachycardia, QT prolongation, sinus tachycardia

Congenital, familial and genetic disorders
Uncommon: Chromosome abnormality

Blood and lymphatic system disorders
Very Common: Neutropenia*, thrombocytopenia*, anaemia*
Common: Febrile neutropenia, pancytopenia, leucopenia*, lymphopenia*
Uncommon: Granulocytopenia, haemolytic anaemia, autoimmune haemolytic anaemia, haemolysis, hypercoagulation, coagulopathy, monocytopenia, leucocytosis, lymphadenopathy

Nervous system disorders
Common: Cerebrovascular accident, syncope, peripheral neuropathy, neuropathy, peripheral sensory neuropathy, dizziness, ageusia, dysgeusia, paraesthesia, headache, tremor*, hypoaesthesia*, somnolence, memory impairment
Uncommon: Intracranial haemorrhage, intracranial venous sinus thrombosis, thrombotic stroke, cerebral ischaemia, transient ischaemic attack, leukoencephalopathy, neurotoxicity, polyneuropathy, peripheral motor neuropathy, dysaesthesia, aphonia, dysphonia,

disturbance in attention, ataxia, balance impaired, postural dizziness, burning sensation, cervical root pain, dyskinesia, hyperaesthesia, motor dysfunction, myasthenic syndrome, oral paraesthesia, psychomotor hyperactivity, anosmia

Eye disorders
Common: Blurred vision, cataract, reduced visual acuity, lacrimation increased
Uncommon: Blindness, retinal arteriosclerosis, retinal vein thrombosis, keratitis, visual disturbance, eyelid oedema, conjunctivitis, eye pruritus, eye redness, eye irritation, dry eye

Ear and labyrinth disorders
Common: Vertigo
Uncommon: Deafness, hypoacusia, tinnitus, ear pain, ear pruritus

Respiratory, thoracic and mediastinal disorders
Common: Pulmonary embolism, dyspnoea*, exertional dyspnoea, bronchitis, cough, pharyngitis, nasopharyngitis, hoarseness, hiccups
Uncommon: Bronchopneumopathy, asthma, respiratory distress, pulmonary congestion, pleuritic pain, nasal congestion, throat secretion increased, laryngitis, sinus congestion, sinus pain, rhinorrhoea, dry throat

Gastrointestinal disorders
Very Common: Constipation, diarrhoea, nausea, increase and decrease in weight
Common: Vomiting, dyspepsia, upper abdominal pain, gastritis, abdominal distension, abdominal pain, stomatitis, dry mouth, flatulence
Uncommon: Gastrointestinal haemorrhage, peptic ulcer haemorrhage, oesophagitis, gastro-oesophageal reflux disease, colitis, caecitis, gastroduodenitis, aptyalism, proctitis, gastroenteritis, oesophageal pain, dysphagia, odynophagia, haemorrhoids, epigastric discomfort, aphthous stomatitis, cheilitis, glossodynia, gingivitis, lip ulceration, tongue ulceration, oral pain, toothache, sensitivity of teeth, gingival bleeding, oral hypoaesthesia, lip pain, coated tongue

Renal and urinary disorders
Common: Renal failure
Uncommon: Acute renal failure, urinary frequency, renal tubular necrosis, cystitis, haematuria, urinary retention, dysuria, acquired Fanconi Syndrome, urinary incontinence, polyuria, increased blood urea, increased blood creatinine, nocturia

Skin and subcutaneous tissue disorders
Very common: Rash*
Common: Face oedema, dry skin, pruritus*, erythema, folliculitis, skin hyperpigmentation, exanthema, increased sweating, night sweats, alopecia
Uncommon: Erythema nodosum, urticaria, eczema, erythrosis, erythematous rash, pruritic rash, papular rash, hyperkeratosis, contusion, skin fissures, acne, dermatitis acneiforme, lichen sclerosus, decubitus ulcer, pigmentation lip, prurigo, rosacea, photosensitivity reaction, seborroeic dermatitis, skin burning sensation, skin desquamation, skin discolouration

Musculoskeletal and connective tissue disorders
Very Common: Muscle cramp*, muscle weakness
Common: Steroid myopathy, myopathy, myalgia, arthralgia, back pain, bone pain, pain in limb, chest wall pain, peripheral swelling
Uncommon: Osteonecrosis, muscle atrophy, amyotrophy, pain in foot, muscle spasms, musculoskeletal pain, night cramps, groin pain, pain in jaw, neck pain, spondylitis, joint stiffness, joint swelling, musculoskeletal stiffness, limb discomfort, toe deformities, local swelling

Endocrine disorders
Common: Cushingoid-like symptoms
Uncommon: Adrenal suppression, adrenal insufficiency, acquired hypothyroidism, increased and decreased thyroid stimulating hormone, hirsutism

Metabolism and nutrition disorders
Common: Hyperglycaemia, anorexia, hypocalcaemia, hypokalaemia, dehydration, hypomagnesaemia, fluid retention
Uncommon: Metabolic acidosis, diabetes mellitus, hyponatraemia, hypercalcaemia, hyperuricaemia, hypoalbuminaemia, cachexia, failure to thrive, gout, hypophosphataemia, hyperphosphataemia, increased appetite

Infections and infestations
Common: Pneumonia*, lower respiratory tract infection, Herpes Zoster, *Herpes Simplex*, urinary tract infection, upper respiratory tract infection, sinusitis, oral candidiasis, oral fungal infection
Uncommon: Septic shock, meningitis, neutropenic sepsis, sepsis, Escherichia sepsis, *Clostridium difficile* sepsis, *Enterobacter* bacteraemia, subacute endocarditis, bronchopneumonia, lobar pneumonia, bacterial pneumonia, pneumococcal pneumonia, *Pneumocystis carinii* pneumonia, primary atypical pneumonia, acute bronchitis, respiratory tract infection, herpes zoster ophthalmic, post-herpetic neuralgia, prostate infection, sinobronchitis, oesophageal candidiasis, infective bursitis, erysipelas, cellulitis, tooth abscess, chronic sinusitis, furuncle, pustular rash, ear infection, fungal infection, genital candidiasis, candida infection, influenza, tinea, fungal foot infection, anal warts

Injury, poisoning and procedural complications
Uncommon: Wound complication

Neoplasms benign, malignant and unspecified (including cysts and polyps)
Uncommon: Basal cell carcinoma, glioblastoma multiforme

Vascular disorders
Common: Deep vein thrombosis*, limb venous thrombosis, hypotension*, hypertension, orthostatic hypotension, flushing
Uncommon: Circulatory collapse, thrombosis, ischaemia, peripheral ischaemia, intermittent claudication, phlebitis, pallor, petechiae, haematoma, postphlebitic syndrome, thrombophlebitis, superficial thrombophlebitis

General disorders and administration site conditions
Very Common: Fatigue*, asthenia*, peripheral oedema
Common: Pyrexia, rigors, mucosal inflammation, oedema, lethargy, malaise
Uncommon: Hyperpyrexia, chest pain, chest tightness, pain, difficulty in walking, abnormal gait, thirst, chest pressure sensation, feeling cold, feeling jittery, influenza-like illness, submandibular mass, fall, impaired healing

Immune system disorders
Uncommon: Acquired hypogammaglobulinaemia

Hepatobiliary disorders
Uncommon: Abnormal liver function tests, increased alanine aminotransferase, increased aspartate aminotransferase, increased blood bilirubin

Reproductive system and breast disorders
Common: Erectile dysfunction, gynaecomastia, metrorrhagia, nipple pain

Psychiatric disorders
Very Common: Insomnia
Common: Confusional state, hallucinations, depression, aggression, agitation, mood alteration, anxiety, nervousness, irritability, mood swings
Uncommon: Psychotic disorder, hypomania, delusion, mental status changes, sleep disorder, abnormal dreams, depressed mood, affect lability, listless, loss of libido, nightmare, personality change, panic attack, restlessness.

4.9 Overdose

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunomodulating agent. ATC code: L04 AX04.

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 multi-centre, 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 (len/dex) 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 (placebo/dex) 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.

Table 1 summarises response rates based on the best response assessments for studies MM-009 and MM-010.

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.

Table 1: Summary of Results of Efficacy Analyses as of Dates Studies Were Unblinded — Pooled Studies MM-009 and MM-010

Endpoint	len/dex (N=353)	placebo/dex (N=351)	Hazard ratio/odds ratio[a], 95% CI, p-value
Median Time To Progression [weeks] [95% CI]	48.3 [41.1, 60.1]	20.1 [19.9, 20.7]	0.35 [0.29, 0.43] p < 0.001 [b]
Overall Response [n, %]	214 (60.6)	77 (21.9)	0.18 [0.13, 0.25], p < 0.001 [c]
Complete Response [n, %]	53 (15.0)	7 (2.0)	0.12 [0.05,0.26], p < 0.001 [c]
Partial Response [n, %]	161 (45.6)	70 (19.9)	0.30 [0.21, 0.42], p < 0.001 [c]
Median Progression Free Survival [weeks] [95% CI]	47.3 [36.9, 58.4]	20.1 [18.1, 20.3]	0.38 [0.32, 0.46] p < 0.001 [b]
1-year Overall Survival rate	82%	75%	0.75 [0.59, 0.95] p = 0.015 [b]

a: Hazard ratio is for TTP, PFS and OS, odds ratio is for response rates. A value below 1 in combination with a P value below 0.025 indicates superiority of len/dex over placebo/dex
b: One-tailed log rank test
c: One tailed continuity-corrected chi-square test

5.2 Pharmacokinetic properties

Lenalidomide has an asymmetric carbon atom and can therefore exist as the optically active forms S(-) and R(+). Lenalidomide is produced as a racemic mixture. Lenalidomide is generally more soluble in organic solvents but exhibits the greatest solubility in 0.1N HCl buffer.

Absorption
Lenalidomide, in healthy volunteers, is rapidly absorbed following oral administration with maximum plasma concentrations occurring between 0.625 and 1.5 hours post-dose. Co-administration with food does not alter the extent of absorption. The maximum concentration (C_{max}) and area-under-the-concentration time curve (AUC) increase proportionately with increases in dose. Multiple dosing does not cause marked drug accumulation. In plasma, the relative exposures of the S- and R- enantiomers of lenalidomide are approximately 56% and 44%, respectively.

Distribution
In vitro (^{14}C)-lenalidomide binding to plasma proteins was low with mean plasma protein binding at 22.7% and 29.2% in multiple myeloma patients and healthy volunteers, respectively.

Metabolism and excretion
In vitro studies indicate that lenalidomide has no inhibitory effect on CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A.

A majority of lenalidomide is eliminated unchanged through urinary excretion. The contribution of renal excretion to total clearance in subjects with normal renal function was 65-85%. The half-life of elimination has been observed to increase with dose, from approximately 3 hours at 5 mg up to approximately 9 hours at doses of 400 mg (the higher dose is believed to provide a better estimate of $t_{½}$). Steady-state levels are achieved by Day 4.

Pharmacokinetics analyses in patients with impaired renal function indicate that as renal function decreases (< 50 ml/min), the total drug clearance decreases proportionally resulting in an increase in AUC. The half-life of lenalidomide increased from approximately 3.5 hours in subjects with creatinine clearance > 50 ml/min to more than 9 hours in subjects with reduced renal function < 50 ml/min. However, renal impairment did not alter the oral absorption of lenalidomide. The C_{max} was similar between healthy subjects and patients with renal impairment. Recommended dose adjustments in patients with impaired renal function are described in section 4.2.

Pharmacokinetic analyses based on multiple myeloma studies indicate that lenalidomide is rapidly absorbed at all dose levels, with maximum plasma concentrations occurring between 0.5 and 4.0 hours post-dose both on Days 1 and 28. The C_{max} and AUC values increase proportionally with dose following single and multiple doses in multiple myeloma patients. Exposure in multiple myeloma patients is slightly higher based on C_{max} and AUC values as compared to healthy male volunteers since the clearance/bioavailable fraction of a drug (CL/F) in multiple myeloma patients is lower (approximately 200 ml/min compared to 300 ml/min) than it is in healthy volunteers. This is consistent with the compromised renal function in the multiple myeloma patients, possibly as a consequence of their age (average patient age of 58 vs. 29 for healthy volunteers) and their disease.

5.3 Preclinical safety data

An embryofoetal development study has been conducted in monkeys administered lenalidomide at doses up to 4 mg/kg/day. Preliminary findings from this on-going study showed that lenalidomide produced malformations (short limbs, bent digits, wrist and/or tail, supernumerary or absent digits) in the offspring of female monkeys who received the drug during pregnancy. Thalidomide produced similar types of malformations in the same study.

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Lenalidomide has a potential for acute toxicity; minimum lethal doses after oral administration were > 2000 mg/kg/day in rodents. 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, 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. 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.

In vitro (bacterial mutation, human lymphocytes, mouse lymphoma, Syrian Hamster Embryo cell transformation) and *in vivo* (rat micronucleus) mutagenicity studies revealed no drug related effects at either the gene or chromosomal level. Carcinogenicity studies with lenalidomide have not been conducted.

Developmental toxicity studies were previously conducted in rabbits. In these studies, rabbits were administered 3, 10 and 20 mg/kg/day orally. 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. Soft tissue and skeletal variations in the foetuses were also observed at 10 and 20 mg/kg/day.

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Deleted: 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.

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Deleted: In rabbits, the maternal and developmental NOAELs for lenalidomide were 3 mg/kg/day corresponding to a safety margin of 1.3 considering a 25 mg/day therapeutic dose.

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6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents:	Lactose, anhydrous Cellulose, microcrystalline Croscarmellose sodium Magnesium stearate
Capsule shell:	Gelatin Titanium dioxide (E171)
Printing ink:	Shellac Propylene glycol Black iron oxide (E172) Potassium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25 C

6.5 Nature and contents of container

The capsules are provided in carton packs. Each pack contains three Polyvinylchloride (PVC) / Polychlorotrifluoroethylene (PCTFE) / Aluminium foil blisters, each with seven capsules. This gives a total of 21 capsules per pack.

6.6 Special precautions for disposal

Unused medicinal product should be returned to the pharmacist.

7. MARKETING AUTHORISATION HOLDER

Celgene Europe Limited
Morgan House
Madeira Walk
Windsor
Berkshire
SL4 1EP
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/391/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14/06/2007

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu/.

1. NAME OF THE MEDICINAL PRODUCT

Revlimid 10 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 10 mg of lenalidomide.

Excipient:
Each capsule contains 294 mg of anhydrous lactose.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

Blue-green/pale yellow capsules marked "REV 10 mg".

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

Administration
Revlimid capsules should be taken at about the same time each day. The capsules should not be broken or chewed. The capsules should be swallowed whole, preferably with water, either with or without food. If less than 12 hours has elapsed since missing a dose, the patient can take the dose. If more than 12 hours has elapsed since missing a dose at the normal time, the patient should not take the dose, but take the next dose at the normal time on the following day.

Recommended dose
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 (see section 4.4).

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

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.

Paediatric patients
There is no experience in children and adolescents. Therefore, lenalidomide should not be used in the paediatric age group (0-17 years).

Elderly patients
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 (see section 5.1). 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.

Use in patients with impaired 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 (CLcr)	Dose Adjustment
Mild renal impairment (CLcr ≥ 50 ml/min)	25 mg once daily (Full Dose)
Moderate renal impairment (30 ≤ CLcr < 50 ml/min)	10 mg once daily*
Severe renal impairment (CLcr < 30 ml/min, not requiring dialysis)	15 mg every other day
End Stage Renal Disease (ESRD) (CLcr < 30 ml/min, requiring dialysis)	15 mg, 3 times a week following each dialysis

* The dose may be escalated to 15 mg once daily after 2 cycles if patient is not responding to treatment and is tolerating the treatment.

Use in patients with impaired hepatic function
Lenalidomide has not formally been studied in patients with impaired hepatic function and there are no specific dose recommendations.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Pregnancy warning
Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. Lenalidomide induced in monkeys malformations similar to those described with thalidomide (see sections 4.6 and 5.3). If lenalidomide is taken during pregnancy, a teratogenic effect of lenalidomide in humans is expected.

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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.

*Amenorrhoea following cancer therapy does not rule out childbearing potential.

Counselling
For women of childbearing potential, lenalidomide is contraindicated unless all of the following are met:
- She understands the expected 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

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- 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.

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 expected 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.

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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 (see also 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 (see 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 mIU/ml must be performed for women of childbearing potential as outlined below. This requirement includes women of childbearing potential who practice absolute and continuous abstinence. Ideally, pregnancy testing, issuing a prescription and dispensing should occur on the same

day. Dispensing of lenalidomide to women of childbearing potential should occur within 7 days of the prescription.

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
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 expected 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 expected 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.

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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 (see 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. A haemoglobin concentration above 13 g/dl should lead to discontinuation of erythropoietic agents. 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; see 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; see section 4.8). Patients should be advised to promptly report febrile episodes. A dose reduction may be required (see 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; see 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 (see 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 (see 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.

Tumour Lysis Syndrome
Because lenalidomide has anti-neoplastic activity the complications of tumour lysis syndrome may occur. The patients at risk of tumour lysis syndrome are those with high tumour burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

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.

4.5 Interaction with other medicinal products and other forms of interaction

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 (see sections 4.4 and 4.8).

Oral contraceptives
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 (see sections 4.4 and 4.6).

Results from human *in vitro* metabolism studies indicate that lenalidomide is not metabolised by cytochrome P450 enzymes suggesting that administration of lenalidomide with drugs that inhibit cytochrome P450 enzymes is not likely to result in metabolic drug interactions in man. *In vitro* studies indicate that lenalidomide has no inhibitory effect on CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A.

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.

4.6 Pregnancy and lactation

Pregnancy (see also sections 4.3 and 4.4)
Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects.

Lenalidomide induced in monkeys malformations similar to those described with thalidomide (see section 5.3). Therefore, a teratogenic effect of lenalidomide is expected and lenalidomide is contraindicated during pregnancy (see section 4.3).

Deleted: The teratogenic effect of lenalidomide cannot be ruled out.¶

Deleted: For lenalidomide no clinical data on exposed pregnancies are available.

Deleted: Studies in animals have shown embryofoetal toxicity

Deleted: thalidomide-like malformations in monkeys

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. If pregnancy occurs in a partner of a male patient taking lenalidomide, it is recommended to refer the female partner 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.

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

4.7 Effects on ability to drive and use machines

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.

4.8 Undesirable effects

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%).

325 (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) (see section 4.4)
- Grade 4 neutropenia (see section 4.4).

The most frequently observed adverse reactions whieh 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 scriousness. 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. Only those adverse reactions marked with * occurred significantly more frequently in the lenalidomide/dexamethasone arm compared to the placebo/dexamethasone arm.

Adverse Drug Reactions (ADRs) observed in patients treated with lenalidomide/dexamethasone:

Investigations
Uncommon: Prolonged prothrombin time, prolonged activated partial thromboplastin time, increased International Normalised Ratio, increased blood alkaline phosphatase, increased blood lactate dehydrogenase, increased C-Reactive Protein, *Cytomegalovirus* antibody positive

Cardiac disorders
Common: Atrial fibrillation, palpitations
Uncommon: Congestive cardiac failure, pulmonary oedema, heart valve insufficiency, atrial flutter, arrhythmia, ventricular trigeminy, bradycardia, tachycardia, QT prolongation, sinus tachycardia

Congenital, familial and genetic disorders
Uncommon: Chromosome abnormality

Blood and lymphatic system disorders
Very Common: Neutropenia*, thrombocytopenia*, anaemia*
Common: Febrile neutropenia, pancytopenia, leucopenia*, lymphopenia*
Uncommon: Granulocytopenia, haemolytic anaemia, autoimmune haemolytic anaemia, haemolysis, hypercoagulation, coagulopathy, monocytopenia, leucocytosis, lymphadenopathy

Nervous system disorders
Common: Cerebrovascular accident, syncope, peripheral neuropathy, neuropathy, peripheral sensory neuropathy, dizziness, ageusia, dysgeusia, paraesthesia, headache, tremor*, hypoaesthesia*, somnolence, memory impairment
Uncommon: Intracranial haemorrhage, intracranial venous sinus thrombosis, thrombotic stroke, cerebral ischaemia, transient ischaemic attack, leukoencephalopathy, neurotoxicity, polyneuropathy, peripheral motor neuropathy, dysaesthesia, aphonia, dysphonia,

disturbance in attention, ataxia, balance impaired, postural dizziness, burning sensation, cervical root pain, dyskinesia, hyperaesthesia, motor dysfunction, myasthenic syndrome, oral paraesthesia, psychomotor hyperactivity, anosmia

Eye disorders
Common: Blurred vision, cataract, reduced visual acuity, lacrimation increased
Uncommon: Blindness, retinal arteriosclerosis, retinal vein thrombosis, keratitis, visual disturbance, eyelid oedema, conjunctivitis, eye pruritus, eye redness, eye irritation, dry eye

Ear and labyrinth disorders
Common: Vertigo
Uncommon: Deafness, hypoacusia, tinnitus, ear pain, ear pruritus

Respiratory, thoracic and mediastinal disorders
Common: Pulmonary embolism, dyspnoea*, exertional dyspnoea, bronchitis, cough, pharyngitis, nasopharyngitis, hoarseness, hiccups
Uncommon: Bronchopneumopathy, asthma, respiratory distress, pulmonary congestion, pleuritic pain, nasal congestion, throat secretion increased, laryngitis, sinus congestion, sinus pain, rhinorrhoea, dry throat

Gastrointestinal disorders
Very Common: Constipation, diarrhoea, nausea, increase and decrease in weight
Common: Vomiting, dyspepsia, upper abdominal pain, gastritis, abdominal distension, abdominal pain, stomatitis, dry mouth, flatulence
Uncommon: Gastrointestinal haemorrhage, peptic ulcer haemorrhage, oesophagitis, gastro-oesophageal reflux disease, colitis, caecitis, gastroduodenitis, aptyalism, proctitis, gastroenteritis, oesophageal pain, dysphagia, odynophagia, haemorrhoids, epigastric discomfort, aphthous stomatitis, cheilitis, glossodynia, gingivitis, lip ulceration, tongue ulceration, oral pain, toothache, sensitivity of teeth, gingival bleeding, oral hypoaesthesia, lip pain, coated tongue

Renal and urinary disorders
Common: Renal failure
Uncommon: Acute renal failure, urinary frequency, renal tubular necrosis, cystitis, haematuria, urinary retention, dysuria, acquired Fanconi Syndrome, urinary incontinence, polyuria, increased blood urea, increased blood creatinine, nocturia

Skin and subcutaneous tissue disorders
Very common: Rash*
Common: Face oedema, dry skin, pruritus*, erythema, folliculitis, skin hyperpigmentation, exanthema, increased sweating, night sweats, alopecia
Uncommon: Erythema nodosum, urticaria, eczema, erythrosis, erythematous rash, pruritic rash, papular rash, hyperkeratosis, contusion, skin fissures, acne, dermatitis acneiforme, lichen sclerosus, decubitus ulcer, pigmentation lip, prurigo, rosacea, photosensitivity reaction, seborroeic dermatitis, skin burning sensation, skin desquamation, skin discolouration

Musculoskeletal and connective tissue disorders
Very Common: Muscle cramp*, muscle weakness
Common: Steroid myopathy, myopathy, myalgia, arthralgia, back pain, bone pain, pain in limb, chest wall pain, peripheral swelling
Uncommon: Osteonecrosis, muscle atrophy, amyotrophy, pain in foot, muscle spasms, musculoskeletal pain, night cramps, groin pain, pain in jaw, neck pain, spondylitis, joint stiffness, joint swelling, musculoskeletal stiffness, limb discomfort, toe deformities, local swelling

Endocrine disorders
Common: Cushingoid-like symptoms
Uncommon: Adrenal suppression, adrenal insufficiency, acquired hypothyroidism, increased and decreased thyroid stimulating hormone, hirsutism

Metabolism and nutrition disorders
Common: Hyperglycaemia, anorexia, hypocalcaemia, hypokalaemia, dehydration, hypomagnesaemia, fluid retention
Uncommon: Metabolic acidosis, diabetes mellitus, hyponatraemia, hypercalcaemia, hyperuricaemia, hypoalbuminaemia, cachexia, failure to thrive, gout, hypophosphataemia, hyperphosphataemia, increased appetite

Infections and infestations
Common: Pneumonia*, lower respiratory tract infection, Herpes Zoster, *Herpes Simplex*, urinary tract infection, upper respiratory tract infection, sinusitis, oral candidiasis, oral fungal infection
Uncommon: Septic shock, meningitis, neutropenic sepsis, sepsis, Escherichia sepsis, *Clostridium difficile* sepsis, *Enterobacter* bacteraemia, subacute endocarditis, bronchopneumonia, lobar pneumonia, bacterial pneumonia, pneumococcal pneumonia, *Pneumocystis carinii* pneumonia, primary atypical pneumonia, acute bronchitis, respiratory tract infection, herpes zoster ophthalmic, post-herpetic neuralgia, prostate infection, sinobronchitis, oesophageal candidiasis, infective bursitis, erysipelas, cellulitis, tooth abscess, chronic sinusitis, furuncle, pustular rash, ear infection, fungal infection, genital candidiasis, candida infection, influenza, tinea, fungal foot infection, anal warts

Injury, poisoning and procedural complications
Uncommon: Wound complication

Neoplasms benign, malignant and unspecified (including cysts and polyps)
Uncommon: Basal cell carcinoma, glioblastoma multiforme

Vascular disorders
Common: Deep vein thrombosis*, limb venous thrombosis, hypotension*, hypertension, orthostatic hypotension, flushing
Uncommon: Circulatory collapse, thrombosis, ischaemia, peripheral ischaemia, intermittent claudication, phlebitis, pallor, petechiae, haematoma, postphlebitic syndrome, thrombophlebitis, superficial thrombophlebitis

General disorders and administration site conditions
Very Common: Fatigue*, asthenia*, peripheral oedema
Common: Pyrexia, rigors, mucosal inflammation, oedema, lethargy, malaise
Uncommon: Hyperpyrexia, chest pain, chest tightness, pain, difficulty in walking, abnormal gait, thirst, chest pressure sensation, feeling cold, feeling jittery, influenza-like illness, submandibular mass, fall, impaired healing

Immune system disorders
Uncommon: Acquired hypogammaglobulinaemia

Hepatobiliary disorders
Uncommon: Abnormal liver function tests, increased alanine aminotransferase, increased aspartate aminotransferase, increased blood bilirubin

Reproductive system and breast disorders
Common: Erectile dysfunction, gynaecomastia, metrorrhagia, nipple pain

Psychiatric disorders

Very Common:	Insomnia
Common:	Confusional state, hallucinations, depression, aggression, agitation, mood alteration, anxiety, nervousness, irritability, mood swings
Uncommon:	Psychotic disorder, hypomania, delusion, mental status changes, sleep disorder, abnormal dreams, depressed mood, affect lability, listless, loss of libido, nightmare, personality change, panic attack, restlessness.

4.9 Overdose

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunomodulating agent. ATC code: L04 AX04.

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 multi-centre, 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 (len/dex) 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 (placebo/dex) 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.

Table 1 summarises response rates based on the best response assessments for studies MM-009 and MM-010.

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.

Table 1: Summary of Results of Efficacy Analyses as of Dates Studies Were Unblinded — Pooled Studies MM-009 and MM-010

Endpoint	len/dex (N=353)	placebo/dex (N=351)	Hazard ratio/odds ratio[a], 95% CI, p-value
Median Time To Progression [weeks] [95% CI]	48.3 [41.1, 60.1]	20.1 [19.9, 20.7]	0.35 [0.29, 0.43] p < 0.001 [b]
Overall Response [n, %]	214 (60.6)	77 (21.9)	0.18 [0.13, 0.25], p < 0.001 [c]
Complete Response [n, %]	53 (15.0)	7 (2.0)	0.12 [0.05,0.26], p < 0.001 [c]
Partial Response [n, %]	161 (45.6)	70 (19.9)	0.30 [0.21, 0.42], p < 0.001 [c]
Median Progression Free Survival [weeks] [95% CI]	47.3 [36.9, 58.4]	20.1 [18.1, 20.3]	0.38 [0.32, 0.46] p < 0.001 [b]
1-year Overall Survival rate	82%	75%	0.75 [0.59, 0.95] p = 0.015 [b]

a: Hazard ratio is for TTP, PFS and OS, odds ratio is for response rates. A value below 1 in combination with a P value below 0.025 indicates superiority of len/dex over placebo/dex
b: One-tailed log rank test
c: One tailed continuity-corrected chi-square test

5.2 Pharmacokinetic properties

Lenalidomide has an asymmetric carbon atom and can therefore exist as the optically active forms S(-) and R(+). Lenalidomide is produced as a racemic mixture. Lenalidomide is generally more soluble in organic solvents but exhibits the greatest solubility in 0.1N HCl buffer.

Absorption
Lenalidomide, in healthy volunteers, is rapidly absorbed following oral administration with maximum plasma concentrations occurring between 0.625 and 1.5 hours post-dose. Co-administration with food does not alter the extent of absorption. The maximum concentration (C_{max}) and area-under-the-concentration time curve (AUC) increase proportionately with increases in dose. Multiple dosing does not cause marked drug accumulation. In plasma, the relative exposures of the S- and R- enantiomers of lenalidomide are approximately 56% and 44%, respectively.

Distribution
In vitro (^{14}C)-lenalidomide binding to plasma proteins was low with mean plasma protein binding at 22.7% and 29.2% in multiple myeloma patients and healthy volunteers, respectively.

Metabolism and excretion
In vitro studies indicate that lenalidomide has no inhibitory effect on CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A.

A majority of lenalidomide is eliminated unchanged through urinary excretion. The contribution of renal excretion to total clearance in subjects with normal renal function was 65-85%. The half-life of elimination has been observed to increase with dose, from approximately 3 hours at 5 mg up to approximately 9 hours at doses of 400 mg (the higher dose is believed to provide a better estimate of $t_{1/2}$). Steady-state levels are achieved by Day 4.

Pharmacokinetics analyses in patients with impaired renal function indicate that as renal function decreases (< 50 ml/min), the total drug clearance decreases proportionally resulting in an increase in AUC. The half-life of lenalidomide increased from approximately 3.5 hours in subjects with creatinine clearance > 50 ml/min to more than 9 hours in subjects with reduced renal function < 50 ml/min. However, renal impairment did not alter the oral absorption of lenalidomide. The C_{max} was similar between healthy subjects and patients with renal impairment. Recommended dose adjustments in patients with impaired renal function are described in section 4.2.

Pharmacokinetic analyses based on multiple myeloma studies indicate that lenalidomide is rapidly absorbed at all dose levels, with maximum plasma concentrations occurring between 0.5 and 4.0 hours post-dose both on Days 1 and 28. The C_{max} and AUC values increase proportionally with dose following single and multiple doses in multiple myeloma patients. Exposure in multiple myeloma patients is slightly higher based on C_{max} and AUC values as compared to healthy male volunteers since the clearance/bioavailable fraction of a drug (CL/F) in multiple myeloma patients is lower (approximately 200 ml/min compared to 300 ml/min) than it is in healthy volunteers. This is consistent with the compromised renal function in the multiple myeloma patients, possibly as a consequence of their age (average patient age of 58 vs. 29 for healthy volunteers) and their disease.

5.3 Preclinical safety data

An embryofoetal development study has been conducted in monkeys administered lenalidomide at doses up to 4 mg/kg/day. Preliminary findings from this on-going study showed that lenalidomide produced malformations (short limbs, bent digits, wrist and/or tail, supernumerary or absent digits) in the offspring of female monkeys who received the drug during pregnancy. Thalidomide produced similar types of malformations in the same study.

Lenalidomide has a potential for acute toxicity; minimum lethal doses after oral administration were > 2000 mg/kg/day in rodents. 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, 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. 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.

In vitro (bacterial mutation, human lymphocytes, mouse lymphoma, Syrian Hamster Embryo cell transformation) and *in vivo* (rat micronucleus) mutagenicity studies revealed no drug related effects at either the gene or chromosomal level. Carcinogenicity studies with lenalidomide have not been conducted.

Developmental toxicity studies were previously conducted in rabbits. In these studies, rabbits were administered 3, 10 and 20 mg/kg/day orally. 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. Soft tissue and skeletal variations in the foetuses were also observed at 10 and 20 mg/kg/day.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents: Lactose, anhydrous
Cellulose, microcrystalline
Croscarmellose sodium
Magnesium stearate

Capsule shell: Gelatin
Titanium dioxide (E171)
Indigo carmine (E132)
Yellow iron oxide (E172)

Printing ink: Shellac
Propylene glycol
Black iron oxide (E172)
Potassium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25 C

6.5 Nature and contents of container

The capsules are provided in carton packs. Each pack contains three Polyvinylchloride (PVC) / Polychlorotrifluoroethylene (PCTFE) / Aluminium foil blisters, each with seven capsules. This gives a total of 21 capsules per pack.

6.6 Special precautions for disposal

Unused medicinal product should be returned to the pharmacist.

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Formatted: Date
Deleted: rats and
Deleted: 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.
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¶
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Deleted: , no limb abnormalities were attributable to lenalidomide.
Deleted: 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)
Deleted: the human relevance of these effects is not known.
Deleted: 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.
Deleted: In rabbits, the maternal and developmental NOAELs for lenalidomide were 3 mg/kg/day corresponding to a safety margin of 1.3 considering a 25 mg/day therapeutic dose.
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7. MARKETING AUTHORISATION HOLDER

Celgene Europe Limited
Morgan House
Madeira Walk
Windsor
Berkshire
SL4 1EP
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/391/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14/06/2007

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu/.

1. NAME OF THE MEDICINAL PRODUCT

Revlimid 15 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 15 mg of lenalidomide.

Excipient:
Each capsule contains 289 mg of anhydrous lactose.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

Pale blue/white capsules marked "REV 15 mg".

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

Administration
Revlimid capsules should be taken at about the same time each day. The capsules should not be broken or chewed. The capsules should be swallowed whole, preferably with water, either with or without food. If less than 12 hours has elapsed since missing a dose, the patient can take the dose. If more than 12 hours has elapsed since missing a dose at the normal time, the patient should not take the dose, but take the next dose at the normal time on the following day.

Recommended dose
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 (see section 4.4).

Lenalidomide treatment must not be started if the Absolute Neutrophil Counts (ANC) $< 1.0 \times 10^9$/l, and/or platelet counts $< 75 \times 10^9$/l or, dependent on bone marrow infiltration by plasma cells, platelet counts $< 30 \times 10^9$/l.

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.

Paediatric patients
There is no experience in children and adolescents. Therefore, lenalidomide should not be used in the paediatric age group (0-17 years).

Elderly patients
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 (see section 5.1). 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.

Use in patients with impaired 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 (CLcr)	Dose Adjustment
Mild renal impairment (CLcr ≥ 50 ml/min)	25 mg once daily (Full Dose)
Moderate renal impairment (30 ≤ CLcr < 50 ml/min)	10 mg once daily*
Severe renal impairment (CLcr < 30 ml/min, not requiring dialysis)	15 mg every other day
End Stage Renal Disease (ESRD) (CLcr < 30 ml/min, requiring dialysis)	15 mg, 3 times a week following each dialysis

* The dose may be escalated to 15 mg once daily after 2 cycles if patient is not responding to treatment and is tolerating the treatment.

Use in patients with impaired hepatic function
Lenalidomide has not formally been studied in patients with impaired hepatic function and there are no specific dose recommendations.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Pregnancy warning
Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. Lenalidomide induced in monkeys malformations similar to those described with thalidomide (see sections 4.6 and 5.3). If lenalidomide is taken during pregnancy, a teratogenic effect of lenalidomide in humans is expected.

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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.

*Amenorrhoea following cancer therapy does not rule out childbearing potential.

Counselling
For women of childbearing potential, lenalidomide is contraindicated unless all of the following are met:
- She understands the expected teratogenic risk to the unborn child

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- 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.

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 expected 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.

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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 (see also 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 (see 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 mIU/ml must be performed for women of childbearing potential as outlined below. This requirement includes women of childbearing potential who practice absolute and continuous abstinence. Ideally, pregnancy testing, issuing a prescription and dispensing should occur on the same

day. Dispensing of lenalidomide to women of childbearing potential should occur within 7 days of the prescription.

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
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 expected 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 expected 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.

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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 (see 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. A haemoglobin concentration above 13 g/dl should lead to discontinuation of erythropoietic agents. 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; see 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; see section 4.8). Patients should be advised to promptly report febrile episodes. A dose reduction may be required (see 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; see 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 (see 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 (see 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.

Tumour Lysis Syndrome
Because lenalidomide has anti-neoplastic activity the complications of tumour lysis syndrome may occur. The patients at risk of tumour lysis syndrome are those with high tumour burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

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.

4.5 Interaction with other medicinal products and other forms of interaction

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 (see sections 4.4 and 4.8).

Oral contraceptives
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 (see sections 4.4 and 4.6).

Results from human *in vitro* metabolism studies indicate that lenalidomide is not metabolised by cytochrome P450 enzymes suggesting that administration of lenalidomide with drugs that inhibit cytochrome P450 enzymes is not likely to result in metabolic drug interactions in man. *In vitro* studies indicate that lenalidomide has no inhibitory effect on CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A.

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.

4.6 Pregnancy and lactation

Pregnancy (see also sections 4.3 and 4.4)
Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects.

Lenalidomide induced in monkeys malformations similar to those described with thalidomide (see section 5.3). Therefore, a teratogenic effect of lenalidomide is expected and lenalidomide is contraindicated during pregnancy (see section 4.3).

Deleted: The teratogenic effect of lenalidomidecannot be ruled out.
Deleted: For lenalidomide no clinical data on exposed pregnancies are available.
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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. If pregnancy occurs in a partner of a male patient taking lenalidomide, it is recommended to refer the female partner 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.

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

4.7 Effects on ability to drive and use machines

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.

4.8 Undesirable effects

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%).

325 (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) (see section 4.4)
- Grade 4 neutropenia (see 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. Only those adverse reactions marked with * occurred significantly more frequently in the lenalidomide/dexamethasone arm compared to the placebo/dexamethasone arm.

Adverse Drug Reactions (ADRs) observed in patients treated with lenalidomide/dexamethasone:

Investigations
Uncommon: Prolonged prothrombin time, prolonged activated partial thromboplastin time, increased International Normalised Ratio, increased blood alkaline phosphatase, increased blood lactate dehydrogenase, increased C-Reactive Protein, *Cytomegalovirus* antibody positive

Cardiac disorders
Common: Atrial fibrillation, palpitations
Uncommon: Congestive cardiac failure, pulmonary oedema, heart valve insufficiency, atrial flutter, arrhythmia, ventricular trigeminy, bradycardia, tachycardia, QT prolongation, sinus tachycardia

Congenital, familial and genetic disorders
Uncommon: Chromosome abnormality

Blood and lymphatic system disorders
Very Common: Neutropenia*, thrombocytopenia*, anaemia*
Common: Febrile neutropenia, pancytopenia, leucopenia*, lymphopenia*
Uncommon: Granulocytopenia, haemolytic anaemia, autoimmune haemolytic anaemia, haemolysis, hypercoagulation, coagulopathy, monocytopenia, leucocytosis, lymphadenopathy

Nervous system disorders
Common: Cerebrovascular accident, syncope, peripheral neuropathy, neuropathy, peripheral sensory neuropathy, dizziness, ageusia, dysgeusia, paraesthesia, headache, tremor*, hypoaesthesia*, somnolence, memory impairment
Uncommon: Intracranial haemorrhage, intracranial venous sinus thrombosis, thrombotic stroke, cerebral ischaemia, transient ischaemic attack, leukoencephalopathy, neurotoxicity, polyneuropathy, peripheral motor neuropathy, dysaesthesia, aphonia, dysphonia,

disturbance in attention, ataxia, balance impaired, postural dizziness, burning sensation, cervical root pain, dyskinesia, hyperaesthesia, motor dysfunction, myasthenic syndrome, oral paraesthesia, psychomotor hyperactivity, anosmia

Eye disorders
Common: Blurred vision, cataract, reduced visual acuity, lacrimation increased
Uncommon: Blindness, retinal arteriosclerosis, retinal vein thrombosis, keratitis, visual disturbance, eyelid oedema, conjunctivitis, eye pruritus, eye redness, eye irritation, dry eye

Ear and labyrinth disorders
Common: Vertigo
Uncommon: Deafness, hypoacusia, tinnitus, ear pain, ear pruritus

Respiratory, thoracic and mediastinal disorders
Common: Pulmonary embolism, dyspnoea*, exertional dyspnoea, bronchitis, cough, pharyngitis, nasopharyngitis, hoarseness, hiccups
Uncommon: Bronchopneumopathy, asthma, respiratory distress, pulmonary congestion, pleuritic pain, nasal congestion, throat secretion increased, laryngitis, sinus congestion, sinus pain, rhinorrhoea, dry throat

Gastrointestinal disorders
Very Common: Constipation, diarrhoea, nausea, increase and decrease in weight
Common: Vomiting, dyspepsia, upper abdominal pain, gastritis, abdominal distension, abdominal pain, stomatitis, dry mouth, flatulence
Uncommon: Gastrointestinal haemorrhage, peptic ulcer haemorrhage, oesophagitis, gastro-oesophageal reflux disease, colitis, caecitis, gastroduodenitis, aptyalism, proctitis, gastroenteritis, oesophageal pain, dysphagia, odynophagia, haemorrhoids, epigastric discomfort, aphthous stomatitis, cheilitis, glossodynia, gingivitis, lip ulceration, tongue ulceration, oral pain, toothache, sensitivity of teeth, gingival bleeding, oral hypoaesthesia, lip pain, coated tongue

Renal and urinary disorders
Common: Renal failure
Uncommon: Acute renal failure, urinary frequency, renal tubular necrosis, cystitis, haematuria, urinary retention, dysuria, acquired Fanconi Syndrome, urinary incontinence, polyuria, increased blood urea, increased blood creatinine, nocturia

Skin and subcutaneous tissue disorders
Very common: Rash*
Common: Face oedema, dry skin, pruritus*, erythema, folliculitis, skin hyperpigmentation, exanthema, increased sweating, night sweats, alopecia
Uncommon: Erythema nodosum, urticaria, eczema, erythrosis, erythematous rash, pruritic rash, papular rash, hyperkeratosis, contusion, skin fissures, acne, dermatitis acneiforme, lichen sclerosus, decubitus ulcer, pigmentation lip, prurigo, rosacea, photosensitivity reaction, seborroele dermatitis, skin burning sensation, skin desquamation, skin discolouration

Musculoskeletal and connective tissue disorders
Very Common: Muscle cramp*, muscle weakness
Common: Steroid myopathy, myopathy, myalgia, arthralgia, back pain, bone pain, pain in limb, chest wall pain, peripheral swelling
Uncommon: Osteonecrosis, muscle atrophy, amyotrophy, pain in foot, muscle spasms, musculoskeletal pain, night cramps, groin pain, pain in jaw, neck pain, spondylitis, joint stiffness, joint swelling, musculoskeletal stiffness, limb discomfort, toe deformities, local swelling

Endocrine disorders
Common: Cushingoid-like symptoms
Uncommon: Adrenal suppression, adrenal insufficiency, acquired hypothyroidism, increased and decreased thyroid stimulating hormone, hirsutism

Metabolism and nutrition disorders
Common: Hyperglycaemia, anorexia, hypocalcaemia, hypokalaemia, dehydration, hypomagnesaemia, fluid retention
Uncommon: Metabolic acidosis, diabetes mellitus, hyponatraemia, hypercalcaemia, hyperuricaemia, hypoalbuminaemia, cachexia, failure to thrive, gout, hypophosphataemia, hyperphosphataemia, increased appetite

Infections and infestations
Common: Pneumonia*, lower respiratory tract infection, Herpes Zoster, *Herpes Simplex*, urinary tract infection, upper respiratory tract infection, sinusitis, oral candidiasis, oral fungal infection
Uncommon: Septic shock, meningitis, neutropenic sepsis, sepsis, Escherichia sepsis, *Clostridium difficile* sepsis, *Enterobacter* bacteraemia, subacute endocarditis, bronchopneumonia, lobar pneumonia, bacterial pneumonia, pneumococcal pneumonia, *Pneumocystis carinii* pneumonia, primary atypical pneumonia, acute bronchitis, respiratory tract infection, herpes zoster ophthalmic, post-herpetic neuralgia, prostate infection, sinobronchitis, oesophageal candidiasis, infective bursitis, erysipelas, cellulitis, tooth abscess, chronic sinusitis, furuncle, pustular rash, ear infection, fungal infection, genital candidiasis, candida infection, influenza, tinea, fungal foot infection, anal warts

Injury, poisoning and procedural complications
Uncommon: Wound complication

Neoplasms benign, malignant and unspecified (including cysts and polyps)
Uncommon: Basal cell carcinoma, glioblastoma multiforme

Vascular disorders
Common: Deep vein thrombosis*, limb venous thrombosis, hypotension*, hypertension, orthostatic hypotension, flushing
Uncommon: Circulatory collapse, thrombosis, ischaemia, peripheral ischaemia, intermittent claudication, phlebitis, pallor, petechiae, haematoma, postphlebitic syndrome, thrombophlebitis, superficial thrombophlebitis

General disorders and administration site conditions
Very Common: Fatigue*, asthenia*, peripheral oedema
Common: Pyrexia, rigors, mucosal inflammation, oedema, lethargy, malaise
Uncommon: Hyperpyrexia, chest pain, chest tightness, pain, difficulty in walking, abnormal gait, thirst, chest pressure sensation, feeling cold, feeling jittery, influenza-like illness, submandibular mass, fall, impaired healing

Immune system disorders
Uncommon: Acquired hypogammaglobulinaemia

Hepatobiliary disorders
Uncommon: Abnormal liver function tests, increased alanine aminotransferase, increased aspartate aminotransferase, increased blood bilirubin

Reproductive system and breast disorders
Common: Erectile dysfunction, gynaecomastia, metrorrhagia, nipple pain

Psychiatric disorders
Very Common: Insomnia
Common: Confusional state, hallucinations, depression, aggression, agitation, mood alteration, anxiety, nervousness, irritability, mood swings
Uncommon: Psychotic disorder, hypomania, delusion, mental status changes, sleep disorder, abnormal dreams, depressed mood, affect lability, listless, loss of libido, nightmare, personality change, panic attack, restlessness.

4.9 Overdose

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunomodulating agent. ATC code: L04 AX04.

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 multi-centre, 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 (len/dex) 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 (placebo/dex) 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.

Table 1 summarises response rates based on the best response assessments for studies MM-009 and MM-010.

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.

Table 1: Summary of Results of Efficacy Analyses as of Dates Studies Were Unblinded — Pooled Studies MM-009 and MM-010

Endpoint	len/dex (N=353)	placebo/dex (N=351)	Hazard ratio/odds ratio[a], 95% CI, p-value
Median Time To Progression [weeks] [95% CI]	48.3 [41.1, 60.1]	20.1 [19.9, 20.7]	0.35 [0.29, 0.43] p < 0.001 [b]
Overall Response [n, %]	214 (60.6)	77 (21.9)	0.18 [0.13, 0.25], p < 0.001 [c]
Complete Response [n, %]	53 (15.0)	7 (2.0)	0.12 [0.05,0.26], p < 0.001 [c]
Partial Response [n, %]	161 (45.6)	70 (19.9)	0.30 [0.21, 0.42], p < 0.001 [c]
Median Progression Free Survival [weeks] [95% CI]	47.3 [36.9, 58.4]	20.1 [18.1, 20.3]	0.38 [0.32, 0.46] p < 0.001 [b]
1-year Overall Survival rate	82%	75%	0.75 [0.59, 0.95] p = 0.015 [b]

a: Hazard ratio is for TTP, PFS and OS, odds ratio is for response rates. A value below 1 in combination with a P value below 0.025 indicates superiority of len/dex over placebo/dex
b: One-tailed log rank test
c: One tailed continuity-corrected chi-square test

5.2 Pharmacokinetic properties

Lenalidomide has an asymmetric carbon atom and can therefore exist as the optically active forms S(-) and R(+). Lenalidomide is produced as a racemic mixture. Lenalidomide is generally more soluble in organic solvents but exhibits the greatest solubility in 0.1N HCl buffer.

Absorption
Lenalidomide, in healthy volunteers, is rapidly absorbed following oral administration with maximum plasma concentrations occurring between 0.625 and 1.5 hours post-dose. Co-administration with food does not alter the extent of absorption. The maximum concentration (C_{max}) and area-under-the-concentration time curve (AUC) increase proportionately with increases in dose. Multiple dosing does not cause marked drug accumulation. In plasma, the relative exposures of the S- and R- enantiomers of lenalidomide are approximately 56% and 44%, respectively.

Distribution
In vitro (^{14}C)-lenalidomide binding to plasma proteins was low with mean plasma protein binding at 22.7% and 29.2% in multiple myeloma patients and healthy volunteers, respectively.

Metabolism and excretion
In vitro studies indicate that lenalidomide has no inhibitory effect on CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A.

A majority of lenalidomide is eliminated unchanged through urinary excretion. The contribution of renal excretion to total clearance in subjects with normal renal function was 65-85%. The half-life of elimination has been observed to increase with dose, from approximately 3 hours at 5 mg up to approximately 9 hours at doses of 400 mg (the higher dose is believed to provide a better estimate of $t_{½}$). Steady-state levels are achieved by Day 4.

Pharmacokinetics analyses in patients with impaired renal function indicate that as renal function decreases (< 50 ml/min), the total drug clearance decreases proportionally resulting in an increase in AUC. The half-life of lenalidomide increased from approximately 3.5 hours in subjects with creatinine clearance > 50 ml/min to more than 9 hours in subjects with reduced renal function < 50 ml/min. However, renal impairment did not alter the oral absorption of lenalidomide. The C_{max} was similar between healthy subjects and patients with renal impairment. Recommended dose adjustments in patients with impaired renal function are described in section 4.2.

Pharmacokinetic analyses based on multiple myeloma studies indicate that lenalidomide is rapidly absorbed at all dose levels, with maximum plasma concentrations occurring between 0.5 and 4.0 hours post-dose both on Days 1 and 28. The C_{max} and AUC values increase proportionally with dose following single and multiple doses in multiple myeloma patients. Exposure in multiple myeloma patients is slightly higher based on C_{max} and AUC values as compared to healthy male volunteers since the clearance/bioavailable fraction of a drug (CL/F) in multiple myeloma patients is lower (approximately 200 ml/min compared to 300 ml/min) than it is in healthy volunteers. This is consistent with the compromised renal function in the multiple myeloma patients, possibly as a consequence of their age (average patient age of 58 vs. 29 for healthy volunteers) and their disease.

5.3 Preclinical safety data

An embryofoetal development study has been conducted in monkeys administered lenalidomide at doses up to 4 mg/kg/day. Preliminary findings from this on-going study showed that lenalidomide produced malformations (short limbs, bent digits, wrist and/or tail, supernumerary or absent digits) in the offspring of female monkeys who received the drug during pregnancy. Thalidomide produced similar types of malformations in the same study.

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Lenalidomide has a potential for acute toxicity; minimum lethal doses after oral administration were > 2000 mg/kg/day in rodents. 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, 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. 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.

In vitro (bacterial mutation, human lymphocytes, mouse lymphoma, Syrian Hamster Embryo cell transformation) and *in vivo* (rat micronucleus) mutagenicity studies revealed no drug related effects at either the gene or chromosomal level. Carcinogenicity studies with lenalidomide have not been conducted.

Developmental toxicity studies were previously conducted in rabbits. In these studie, rabbits were administered 3, 10 and 20 mg/kg/day orally. 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. Soft tissue and skeletal variations in the foetuses were also observed at 10 and 20 mg/kg/day.

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¶
¶

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Deleted: In rats, lenalidomide was not teratogenic at oral doses of up to 500 mg/kg/day. Nevertheless,

Deleted: rat species is not considered as a relevant model for thalidomide analogues.

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Deleted: , no limb abnormalities were attributable to lenalidomide

Deleted: 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).

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Deleted: 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.

Deleted: In rabbits, the maternal and developmental NOAELs for lenalidomide were 3 mg/kg/day corresponding to a safety margin of 1.3 considering a 25 mg/day therapeutic dose.¶

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6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents: Lactose, anhydrous
Cellulose, microcrystalline
Croscarmellose sodium
Magnesium stearate

Capsule shell: Gelatin
Titanium dioxide (E171)
Indigo carmine (E132)

Printing ink: Shellac
Propylene glycol
Black iron oxide (E172)
Potassium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25 C

6.5 Nature and contents of container

The capsules are provided in carton packs. Each pack contains three Polyvinylchloride (PVC) / Polychlorotrifluoroethylene (PCTFE) / Aluminium foil blisters, each with seven capsules. This gives a total of 21 capsules per pack.

6.6 Special precautions for disposal

Unused medicinal product should be returned to the pharmacist.

7. MARKETING AUTHORISATION HOLDER

Celgene Europe Limited
Morgan House
Madeira Walk
Windsor
Berkshire
SL4 1EP
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/391/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14/06/2007

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu/.

1. NAME OF THE MEDICINAL PRODUCT

Revlimid 25 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 25 mg of lenalidomide.

Excipient:
Each capsule contains 200 mg of anhydrous lactose.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

White capsules marked "REV 25 mg".

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

Administration
Revlimid capsules should be taken at about the same time each day. The capsules should not be broken or chewed. The capsules should be swallowed whole, preferably with water, either with or without food. If less than 12 hours has elapsed since missing a dose, the patient can take the dose. If more than 12 hours has elapsed since missing a dose at the normal time, the patient should not take the dose, but take the next dose at the normal time on the following day.

Recommended dose
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 (see section 4.4).

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

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.

Paediatric patients
There is no experience in children and adolescents. Therefore, lenalidomide should not be used in the paediatric age group (0-17 years).

Elderly patients
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 (see section 5.1). 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.

Use in patients with impaired 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 (CLcr)	Dose Adjustment
Mild renal impairment (CLcr ≥ 50 ml/min)	25 mg once daily (Full Dose)
Moderate renal impairment (30 ≤ CLcr < 50 ml/min)	10 mg once daily*
Severe renal impairment (CLcr < 30 ml/min, not requiring dialysis)	15 mg every other day
End Stage Renal Disease (ESRD) (CLcr < 30 ml/min, requiring dialysis)	15 mg, 3 times a week following each dialysis

* The dose may be escalated to 15 mg once daily after 2 cycles if patient is not responding to treatment and is tolerating the treatment.

Use in patients with impaired hepatic function
Lenalidomide has not formally been studied in patients with impaired hepatic function and there are no specific dose recommendations.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Pregnancy warning
Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. Lenalidomide induced in monkeys malformations similar to those described with thalidomide (see sections 4.6 and 5.3). If lenalidomide is taken during pregnancy, a teratogenic effect of lenalidomide in humans is expected.

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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.

*Amenorrhoea following cancer therapy does not rule out childbearing potential.

Counselling
For women of childbearing potential, lenalidomide is contraindicated unless all of the following are met:
- She understands the expected 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

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- 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 bazards and necessary precautions associated with the use of lenalidomide.

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 expected 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.

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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 (see also 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 (see 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 mIU/ml must be performed for women of childbearing potential as outlined below. This requirement includes women of childbearing potential who practice absolute and continuous abstinence. Ideally, pregnancy testing, issuing a prescription and dispensing should occur on the same

day. Dispensing of lenalidomide to women of childbearing potential should occur within 7 days of the prescription.

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
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 expected 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 expected 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.

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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 (see 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. A haemoglobin concentration above 13 g/dl should lead to discontinuation of erythropoietic agents. 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; see 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; see section 4.8). Patients should be advised to promptly report febrile episodes. A dose reduction may be required (see 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; see 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 (see 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 (see 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.

Tumour Lysis Syndrome
Because lenalidomide has anti-neoplastic activity the complications of tumour lysis syndrome may occur. The patients at risk of tumour lysis syndrome are those with high tumour burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

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.

4.5 Interaction with other medicinal products and other forms of interaction

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 (see sections 4.4 and 4.8).

Oral contraceptives
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 (see sections 4.4 and 4.6).

Results from human *in vitro* metabolism studies indicate that lenalidomide is not metabolised by cytochrome P450 enzymes suggesting that administration of lenalidomide with drugs that inhibit cytochrome P450 enzymes is not likely to result in metabolic drug interactions in man. *In vitro* studies indicate that lenalidomide has no inhibitory effect on CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A.

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.

4.6 Pregnancy and lactation

Pregnancy (see also sections 4.3 and 4.4)
Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects.

Lenalidomide induced in monkeys malformations similar to those described with thalidomide (see section 5.3). Therefore, a teratogenic effect of lenalidomide is expected and lenalidomide is contraindicated during pregnancy (see section 4.3).

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Deleted: For lenalidomide no clinical data on exposed pregnancies are available.

Deleted: Studies in animals have shown embryofoetal toxicity

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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. If pregnancy occurs in a partner of a male patient taking lenalidomide, it is recommended to refer the female partner 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.

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

4.7 Effects on ability to drive and use machines

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.

4.8 Undesirable effects

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%).

325 (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) (see section 4.4)
- Grade 4 neutropenia (see 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. Only those adverse reactions marked with * occurred significantly more frequently in the lenalidomide/dexamethasone arm compared to the placebo/dexamethasone arm.

Adverse Drug Reactions (ADRs) observed in patients treated with lenalidomide/dexamethasone:

Investigations
Uncommon: Prolonged prothrombin time, prolonged activated partial thromboplastin time, increased International Normalised Ratio, increased blood alkaline phosphatase, increased blood lactate dehydrogenase, increased C-Reactive Protein, *Cytomegalovirus* antibody positive

Cardiac disorders
Common: Atrial fibrillation, palpitations
Uncommon: Congestive cardiac failure, pulmonary oedema, heart valve insufficiency, atrial flutter, arrhythmia, ventricular trigeminy, bradycardia, tachycardia, QT prolongation, sinus tachycardia

Congenital, familial and genetic disorders
Uncommon: Chromosome abnormality

Blood and lymphatic system disorders
Very Common: Neutropenia*, thrombocytopenia*, anaemia*
Common: Febrile neutropenia, pancytopenia, leucopenia*, lymphopenia*
Uncommon: Granulocytopenia, haemolytic anaemia, autoimmune haemolytic anaemia, haemolysis, hypercoagulation, coagulopathy, monocytopenia, leucocytosis, lymphadenopathy

Nervous system disorders
Common: Cerebrovascular accident, syncope, peripheral neuropathy, neuropathy, peripheral sensory neuropathy, dizziness, ageusia, dysgeusia, paraesthesia, headache, tremor*, hypoaesthesia*, somnolence, memory impairment
Uncommon: Intracranial haemorrhage, intracranial venous sinus thrombosis, thrombotic stroke, cerebral ischaemia, transient ischaemic attack, leukoencephalopathy, neurotoxicity, polyneuropathy, peripheral motor neuropathy, dysaesthesia, aphonia, dysphonia,

disturbance in attention, ataxia, balance impaired, postural dizziness, burning sensation, cervical root pain, dyskinesia, hyperaesthesia, motor dysfunction, myasthenic syndrome, oral paraesthesia, psychomotor hyperactivity, anosmia

Eye disorders
Common: Blurred vision, cataract, reduced visual acuity, lacrimation increased
Uncommon: Blindness, retinal arteriosclerosis, retinal vein thrombosis, keratitis, visual disturbance, eyelid oedema, conjunctivitis, eye pruritus, eye redness, eye irritation, dry eye

Ear and labyrinth disorders
Common: Vertigo
Uncommon: Deafness, hypoacusia, tinnitus, ear pain, ear pruritus

Respiratory, thoracic and mediastinal disorders
Common: Pulmonary embolism, dyspnoea*, exertional dyspnoea, bronchitis, cough, pharyngitis, nasopharyngitis, hoarseness, hiccups
Uncommon: Bronchopneumopathy, asthma, respiratory distress, pulmonary congestion, pleuritic pain, nasal congestion, throat secretion increased, laryngitis, sinus congestion, sinus pain, rhinorrhoea, dry throat

Gastrointestinal disorders
Very Common: Constipation, diarrhoea, nausea, increase and decrease in weight
Common: Vomiting, dyspepsia, upper abdominal pain, gastritis, abdominal distension, abdominal pain, stomatitis, dry mouth, flatulence
Uncommon: Gastrointestinal haemorrhage, peptic ulcer haemorrhage, oesophagitis, gastro-oesophageal reflux disease, colitis, caecitis, gastroduodenitis, aptyalism, proctitis, gastroenteritis, oesophageal pain, dysphagia, odynophagia, haemorrhoids, epigastric discomfort, aphthous stomatitis, cheilitis, glossodynia, gingivitis, lip ulceration, tongue ulceration, oral pain, toothache, sensitivity of teeth, gingival bleeding, oral hypoaesthesia, lip pain, coated tongue

Renal and urinary disorders
Common: Renal failure
Uncommon: Acute renal failure, urinary frequency, renal tubular necrosis, cystitis, haematuria, urinary retention, dysuria, acquired Fanconi Syndrome, urinary incontinence, polyuria, increased blood urea, increased blood creatinine, nocturia

Skin and subcutaneous tissue disorders
Very common: Rash*
Common: Face oedema, dry skin, pruritus*, erythema, folliculitis, skin hyperpigmentation, exanthema, increased sweating, night sweats, alopecia
Uncommon: Erythema nodosum, urticaria, eczema, erythrosis, erythematous rash, pruritic rash, papular rash, hyperkeratosis, contusion, skin fissures, acne, dermatitis acneiforme, lichen sclerosus, decubitus ulcer, pigmentation lip, prurigo, rosacea, photosensitivity reaction, seborroeic dermatitis, skin burning sensation, skin desquamation, skin discolouration

Musculoskeletal and connective tissue disorders
Very Common: Muscle cramp*, muscle weakness
Common: Steroid myopathy, myopathy, myalgia, arthralgia, back pain, bone pain, pain in limb, chest wall pain, peripheral swelling
Uncommon: Osteonecrosis, muscle atrophy, amyotrophy, pain in foot, muscle spasms, musculoskeletal pain, night cramps, groin pain, pain in jaw, neck pain, spondylitis, joint stiffness, joint swelling, musculoskeletal stiffness, limb discomfort, toe deformities, local swelling

Endocrine disorders
Common: Cushingoid-like symptoms
Uncommon: Adrenal suppression, adrenal insufficiency, acquired hypothyroidism, increased and decreased thyroid stimulating hormone, hirsutism

Metabolism and nutrition disorders
Common: Hyperglycaemia, anorexia, hypocalcaemia, hypokalaemia, dehydration, hypomagnesaemia, fluid retention
Uncommon: Metabolic acidosis, diabetes mellitus, hyponatraemia, hypercalcaemia, hyperuricaemia, hypoalbuminaemia, cachexia, failure to thrive, gout, hypophosphataemia, hyperphosphataemia, increased appetite

Infections and infestations
Common: Pneumonia*, lower respiratory tract infection, Herpes Zoster, *Herpes Simplex*, urinary tract infection, upper respiratory tract infection, sinusitis, oral candidiasis, oral fungal infection
Uncommon: Septic shock, meningitis, neutropenic sepsis, sepsis, Escherichia sepsis, *Clostridium difficile* sepsis, *Enterobacter* bacteraemia, subacute endocarditis, bronchopneumonia, lobar pneumonia, bacterial pneumonia, pneumococcal pneumonia, *Pneumocystis carinii* pneumonia, primary atypical pneumonia, acute bronchitis, respiratory tract infection, herpes zoster ophthalmic, post-herpetic neuralgia, prostate infection, sinobronchitis, oesophageal candidiasis, infective bursitis, erysipelas, cellulitis, tooth abscess, chronic sinusitis, furuncle, pustular rash, ear infection, fungal infection, genital candidiasis, candida infection, influenza, tinea, fungal foot infection, anal warts

Injury, poisoning and procedural complications
Uncommon: Wound complication

Neoplasms benign, malignant and unspecified (including cysts and polyps)
Uncommon: Basal cell carcinoma, glioblastoma multiforme

Vascular disorders
Common: Deep vein thrombosis*, limb venous thrombosis, hypotension*, hypertension, orthostatic hypotension, flushing
Uncommon: Circulatory collapse, thrombosis, ischaemia, peripheral ischaemia, intermittent claudication, phlebitis, pallor, petechiae, haematoma, postphlebitic syndrome, thrombophlebitis, superficial thrombophlebitis

General disorders and administration site conditions
Very Common: Fatigue*, asthenia*, peripheral oedema
Common: Pyrexia, rigors, mucosal inflammation, oedema, lethargy, malaise
Uncommon: Hyperpyrexia, chest pain, chest tightness, pain, difficulty in walking, abnormal gait, thirst, chest pressure sensation, feeling cold, feeling jittery, influenza-like illness, submandibular mass, fall, impaired healing

Immune system disorders
Uncommon: Acquired hypogammaglobulinaemia

Hepatobiliary disorders
Uncommon: Abnormal liver function tests, increased alanine aminotransferase, increased aspartate aminotransferase, increased blood bilirubin

Reproductive system and breast disorders
Common: Erectile dysfunction, gynaecomastia, metrorrhagia, nipple pain

Psychiatric disorders

Very Common:	Insomnia
Common:	Confusional state, hallucinations, depression, aggression, agitation, mood alteration, anxiety, nervousness, irritability, mood swings
Uncommon:	Psychotic disorder, hypomania, delusion, mental status changes, sleep disorder, abnormal dreams, depressed mood, affect lability, listless, loss of libido, nightmare, personality change, panic attack, restlessness.

4.9 Overdose

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunomodulating agent. ATC code: L04 AX04.

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 multi-centre, 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 (len/dex) 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 (placebo/dex) 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.

Table 1 summarises response rates based on the best response assessments for studies MM-009 and MM-010.

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.

Table 1: Summary of Results of Efficacy Analyses as of Dates Studies Were Unblinded — Pooled Studies MM-009 and MM-010

Endpoint	len/dex (N=353)	placebo/dex (N=351)	Hazard ratio/odds ratio[a], 95% CI, p-value
Median Time To Progression [weeks] [95% CI]	48.3 [41.1, 60.1]	20.1 [19.9, 20.7]	0.35 [0.29, 0.43] p < 0.001 [b]
Overall Response [n, %]	214 (60.6)	77 (21.9)	0.18 [0.13, 0.25], p < 0.001 [c]
Complete Response [n, %]	53 (15.0)	7 (2.0)	0.12 [0.05,0.26], p < 0.001 [c]
Partial Response [n, %]	161 (45.6)	70 (19.9)	0.30 [0.21, 0.42], p < 0.001 [c]
Median Progression Free Survival [weeks] [95% CI]	47.3 [36.9, 58.4]	20.1 [18.1, 20.3]	0.38 [0.32, 0.46] p < 0.001 [b]
1-year Overall Survival rate	82%	75%	0.75 [0.59, 0.95] p = 0.015 [b]

a: Hazard ratio is for TTP, PFS and OS, odds ratio is for response rates. A value below 1 in combination with a P value below 0.025 indicates superiority of len/dex over placebo/dex
b: One-tailed log rank test
c: One tailed continuity-corrected chi-square test

5.2 Pharmacokinetic properties

Lenalidomide has an asymmetric carbon atom and can therefore exist as the optically active forms S(-) and R(+). Lenalidomide is produced as a racemic mixture. Lenalidomide is generally more soluble in organic solvents but exhibits the greatest solubility in 0.1N HCl buffer.

Absorption
Lenalidomide, in healthy volunteers, is rapidly absorbed following oral administration with maximum plasma concentrations occurring between 0.625 and 1.5 hours post-dose. Co-administration with food does not alter the extent of absorption. The maximum concentration (C_{max}) and area-under-the-concentration time curve (AUC) increase proportionately with increases in dose. Multiple dosing does not cause marked drug accumulation. In plasma, the relative exposures of the S- and R- enantiomers of lenalidomide are approximately 56% and 44%, respectively.

Distribution
In vitro (^{14}C)-lenalidomide binding to plasma proteins was low with mean plasma protein binding at 22.7% and 29.2% in multiple myeloma patients and healthy volunteers, respectively.

Metabolism and excretion
In vitro studies indicate that lenalidomide has no inhibitory effect on CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A.

A majority of lenalidomide is eliminated unchanged through urinary excretion. The contribution of renal excretion to total clearance in subjects with normal renal function was 65-85%. The half-life of elimination has been observed to increase with dose, from approximately 3 hours at 5 mg up to approximately 9 hours at doses of 400 mg (the higher dose is believed to provide a better estimate of $t_{½}$). Steady-state levels are achieved by Day 4.

Pharmacokinetics analyses in patients with impaired renal function indicate that as renal function decreases (< 50 ml/min), the total drug clearance decreases proportionally resulting in an increase in AUC. The half-life of lenalidomide increased from approximately 3.5 hours in subjects with creatinine clearance > 50 ml/min to more than 9 hours in subjects with reduced renal function < 50 ml/min. However, renal impairment did not alter the oral absorption of lenalidomide. The C_{max} was similar between healthy subjects and patients with renal impairment. Recommended dose adjustments in patients with impaired renal function are described in section 4.2.

Pharmacokinetic analyses based on multiple myeloma studies indicate that lenalidomide is rapidly absorbed at all dose levels, with maximum plasma concentrations occurring between 0.5 and 4.0 hours post-dose both on Days 1 and 28. The C_{max} and AUC values inerease proportionally with dose following single and multiple doses in multiple myeloma patients. Exposure in multiple myeloma patients is slightly higher based on C_{max} and AUC values as compared to healthy male volunteers since the clearance/bioavailable fraction of a drug (CL/F) in multiple myeloma patients is lower (approximately 200 ml/min compared to 300 ml/min) than it is in healthy volunteers. This is consistent with the compromised renal function in the multiple myeloma patients, possibly as a consequence of their age (average patient age of 58 vs. 29 for healthy volunteers) and their disease.

5.3 Preclinical safety data

An embryofoetal development study has been conducted in monkeys administered lenalidomide at doses up to 4 mg/kg/day. Preliminary findings from this on-going study showed that lenalidomide produced malformations (short limbs, bent digits, wrist and/or tail, supernumerary or absent digits) in the offspring of female monkeys who received the drug during pregnancy. Thalidomide produced similar types of malformations in the same study.

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Lenalidomide has a potential for acute toxicity; minimum lethal doses after oral administration were > 2000 mg/kg/day in rodents. 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, 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. 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.

In vitro (bacterial mutation, human lymphocytes, mouse lymphoma, Syrian Hamster Embryo cell transformation) and *in vivo* (rat micronucleus) mutagenicity studies revealed no drug related effects at either the gene or chromosomal level. Carcinogenicity studies with lenalidomide have not been conducted.

Developmental toxicity studies were previously conducted in rabbits. In these studies, rabbits were administered 3, 10 and 20 mg/kg/day orally. 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. Soft tissue and skeletal variations in the foetuses were also observed at 10 and 20 mg/kg/day.

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Deleted: The human relevance of these effects is not known.
Deleted: 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.
Deleted: In rabbits, the maternal and developmental NOAELs for lenalidomide were 3 mg/kg/day corresponding to a safety margin of 1.3 considering a 25 mg/day therapeutic dose.¶
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6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents: Lactose, anhydrous
Cellulose, microcrystalline
Croscarmellose sodium
Magnesium stearate

Capsule shell: Gelatin
Titanium dioxide (E171)

Printing ink: Shellac
Propylene glycol
Black iron oxide (E172)
Potassium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25 C

6.5 Nature and contents of container

The capsules are provided in carton packs. Each pack contains three Polyvinylchloride (PVC) / Polychlorotrifluoroethylene (PCTFE) / Aluminium foil blisters, each with seven capsules. This gives a total of 21 capsules per pack.

6.6 Special precautions for disposal

Unused medicinal product should be returned to the pharmacist.

7. MARKETING AUTHORISATION HOLDER

Celgene Europe Limited

Morgan House
Madeira Walk
Windsor
Berkshire
SL4 1EP
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/391/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14/06/2007

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu/.

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Penn Pharmaceutical Services Limited
Tafarnaubach Industrial Estate
Tredegar, Gwent NP2 3AA
United Kingdom

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

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

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

1. The MAH shall agree the details of a controlled distribution system with the National Competent Authorities and must implement such programme nationally to ensure that:
   - Prior to launch, all doctors who intend to prescribe Revlimid and all pharmacists who may dispense Revlimid receive a Direct Healthcare Professional Communication as described below.
   - Prior to prescribing (where appropriate, and in agreement with the National Competent Authority, dispensing) all healthcare professionals who intend to prescribe (and dispense) Revlimid are provided with a physician information pack containing the following:
     - Educational Health Care Professional's kit
     - Educational brochures for Patients
     - Patient cards
     - Summary of Product Characteristics (SPC) and Package Leaflet and Labelling.

2. The MAH shall implement a pregnancy prevention programme (PPP) in each Member State. Details of the PPP should be agreed with the National Competent Authorities in each Member State and put in place prior to the marketing of the product.

3. The MAH should agree the final text of the Direct Healthcare Professional Communication and the physician information pack contents with the National Competent Authority in each Member State and ensure that the materials contain the key elements as described below.

4. The MAH should agree on the implementation of the patient card system in each Member State.

5. The MAH should also agree with each Member State prior to the launch of the product:
   - The feasibility of collecting detailed data relating to the indication in order to monitor closely the off-label use within the national territory
   - The set-up of national measures to assess the effectiveness of and compliance with the PPP.

Key elements to be included

Direct Healthcare Professional Communication

The Direct Healthcare Professional Communication shall consist of two parts:
- A core text as agreed by the CHMP.
- National specific requirements agreed with the National Competent Authority regarding:

  - Distribution of the product
  - To ensure that all appropriate measures have been performed prior to Revlimid being dispensed

The Educational Healthcare Professional's Kit

The Educational Health Care Professional's Kit shall contain the following elements:
- Brief background on lenalidomide and its licensed indication
- Posology
- The need to avoid foetal exposure due to teratogenicity of lenalidomide in animals and the expected teratogenic effect of lenalidomide in humans including a summary of the interim results of study CC-5013-TOX-004
- Obligations of the health care professional in relation to the prescribing of Revlimid
  - Need to provide comprehensive advice and counselling to patients
  - That patients should be capable of complying with the requirements for the safe use of Revlimid
  - Need to provide patients with appropriate patient educational brochure and patient card
- Safety advice relevant to all patients
  - Description and management of neutropenia and thrombocytopenia including incidence rates from clinical trials
  - Description and management of thromboembolic risk including incidence rates from clinical trials
  - Use in patients with hepatic and/or renal impairment
  - Disposal of unwanted medicine
  - Local country specific arrangements for a prescription for Revlimid to be dispensed
  - Description of risk of hypothyroidism
  - Explanation of unknown risk of neuropathy with long term use
- Description of the PPP and categorisation of patients based on sex and childbearing potential
  - Algorithm for implementation of PPP
  - Definition of women of childbearing potential (WCBP) and actions the physician should take if unsure
- Safety advice for women of childbearing potential
  - The need to avoid foetal exposure
  - Description of the PPP
  - Need for adequate contraception (even if woman has amenorrhoea) and definition of adequate contraception
  - Pregnancy test regime
    - Advice on suitable tests
    - Before commencing treatment
    - During treatment based on method of contraception
    - After finishing treatment
  - Need to stop Revlimid immediately upon suspicion of pregnancy
  - Need to tell treating doctor immediately upon suspicion of pregnancy
- Safety advice for men
  - The need to avoid foetal exposure
  - The need to use condoms if sexual partner is a WCBP (even if man has had a vasectomy)
    - During Revlimid treatment
    - For one week following final dose.
  - That if his partner becomes pregnant whilst he is taking Revlimid or shortly after he has stopped taking Revlimid he should inform his treating doctor immediately
- Requirements in the event of pregnancy
  - Instructions to stop Revlimid immediately upon suspicion of pregnancy
  - Need to refer to physician specialised or experienced in dealing with teratology and its diagnosis for evaluation and advice
  - Local contact details for reporting of any suspected pregnancy

- Pregnancy reporting form
- Check list for physicians ensuring that patients receive the appropriate counselling concerning the treatment, contraceptive methods and pregnancy prevention appropriate for their sex and childbearing status
- Adverse event reporting forms

Educational Brochures for patients

The Educational brochures for patients should be of 3 types:
- Brochure for women patients of childbearing potential and their partners
- Brochure for women patients who are not of childbearing potential
- Brochure for male patients

All patient brochures should contain the following elements:
- That lenalidomide is teratogenic in animals and is expected to be teratogenic in humans
- That Revlimid may cause neutropenia and thrombocytopenia and the need for regular blood tests
- Description of the patient card and its necessity
- Disposal of unwanted medicine
- National or other applicable specific arrangements for a prescription for Revlimid to be dispensed
- That the patient should not give Revlimid to any other person
- That the patient should not donate blood
- That the patient should tell their doctor about any adverse events

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The following information should also be provided in the appropriate brochure:

Brochure for women patients with childbearing potential
- The need to avoid foetal exposure
- Description of the PPP
- Need for adequate contraception and definition of adequate contraception
- Pregnancy test regime
  - Before commencing treatment
  - During treatment, every 4 weeks except in case of confirmed tubal sterilisation
  - After finishing treatment
- The need to stop Revlimid immediately upon suspicion of pregnancy
- The need to contact their doctor immediately upon suspicion of pregnancy

Brochure for male patients
- The need to avoid foetal exposure
- The need to use condoms if sexual partner is a WCBP (even if man has had vasectomy)
  - During Revlimid treatment
  - For one week following final dose
- That the patient should not donate semen
- That if his partner becomes pregnant he should inform his treating doctor immediately

Patient Card

The patient card shall contain the following elements:
- Verification that appropriate counselling has taken place
- Documentation of childbearing status potential
- Pregnancy test dates and results

- **OTHER CONDITIONS**

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance, as described in version 2.0 presented in module 1.8.1 of the Marketing Authorisation Application, is in place and functioning before the product is placed on the market.

Risk Management Plan

The MAH commits to perform the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan as agreed in version 8.3 of the Risk Management Plan (RMP) presented in module 1.8.2 of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

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As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:
- when new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- within 60 days of an important (Pharmacovigilance or risk minimisation) milestone being reached
- at the request of the EMEA.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Revlimid 5 mg hard capsules
lenalidomide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 5 mg lenalidomide.

3. LIST OF EXCIPIENTS

It contains lactose, anhydrous.
See package leaflet, section 2.

4. PHARMACEUTICAL FORM AND CONTENTS

21 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Use only as directed by your doctor.

Lenalidomide is expected to be harmful to an unborn child.

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8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Unused medicinal product should be returned to the pharmacist.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Celgene Europe Limited
Morgan House
Madeira Walk
Windsor
Berkshire
SL4 1EP
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/391/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Revlimid 5 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

1. NAME OF THE MEDICINAL PRODUCT

Revlimid 5 mg hard capsules
lenalidomide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Celgene Europe Ltd.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Revlimid 10 mg hard capsules
lenalidomide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 10 mg lenalidomide.

3. LIST OF EXCIPIENTS

It contains lactose, anhydrous.
See package leaflet, section 2.

4. PHARMACEUTICAL FORM AND CONTENTS

21 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Use only as directed by your doctor.

Lenalidomide is expected to be harmful to an unborn child.

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8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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SL4 1EP
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/391/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Revlimid 10 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

1. NAME OF THE MEDICINAL PRODUCT

Revlimid 10 mg hard capsules
lenalidomide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Celgene Europe Ltd.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Revlimid 15 mg hard capsules
lenalidomide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 15 mg lenalidomide.

3. LIST OF EXCIPIENTS

It contains lactose, anhydrous.
See package leaflet, section 2.

4. PHARMACEUTICAL FORM AND CONTENTS

21 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Use only as directed by your doctor.

Lenalidomide is expected to be harmful to an unborn child. Deleted: may

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Unused medicinal product should be returned to the pharmacist.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Celgene Europe Limited
Morgan House
Madeira Walk
Windsor
Berkshire
SL4 1EP
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/391/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Revlimid 15 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

1. NAME OF THE MEDICINAL PRODUCT

Revlimid 15 mg hard capsules
lenalidomide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Celgene Europe Ltd.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Revlimid 25 mg hard capsules
lenalidomide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 25 mg lenalidomide.

3. LIST OF EXCIPIENTS

It contains lactose, anhydrous.
See package leaflet, see section 2.

4. PHARMACEUTICAL FORM AND CONTENTS

21 hard capsule

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Use only as directed by your doctor.

Lenalidomide is expected to be harmful to an unborn child.

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8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Unused medicinal product should be returned to the pharmacist.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Celgene Europe Limited
Morgan House
Madeira Walk
Windsor
Berkshire
SL4 1EP
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/391/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Revlimid 25 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

1. NAME OF THE MEDICINAL PRODUCT

Revlimid 25 mg hard capsules
lenalidomide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Celgene Europe Ltd.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Revlimid 5 mg hard capsules
Revlimid 10 mg hard capsules
Revlimid 15 mg hard capsules
Revlimid 25 mg hard capsules
lenalidomide

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- **This medicine has been prescribed for you. Do not pass it on or share it with others. It may harm them, even if their symptoms are the same as yours.**
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet

1. WHAT REVLIMID IS AND WHAT IT IS USED FOR

What Revlimid is
Revlimid belongs to a group of medicines called immunomodulatory medicines, which can modify or regulate the functioning of the immune system.

What Revlimid is used for
Revlimid in combination with dexamethasone is used to treat adult patients who have been diagnosed with multiple myeloma. Multiple myeloma is a type of blood cancer that affects the white blood cells that produce antibodies.

2. BEFORE YOU TAKE REVLIMID

Follow all of your doctor's instructions carefully, even if they differ from the general information given in this leaflet.

DO NOT TAKE Revlimid

- if you are pregnant or think you may be pregnant or are planning to become pregnant, **as Revlimid is expected to be harmful to an unborn child** (see section 2, "Take special care with Revlimid" and "Pregnancy").
- if you are able to become pregnant, unless you follow all the necessary measures to prevent you from becoming pregnant (see section 2 "Take special care with Revlimid" and "Pregnancy"). If you are able to become pregnant, your doctor will record with each prescription that the necessary measures have been taken and will provide you with this confirmation.
- if you are allergic (hypersensitive) to lenalidomide or any of the other ingredients of Revlimid listed in Section 6, "What Revlimid contains". If you think you may be allergic, ask your doctor for advice.

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If any of these apply to you, tell your doctor before you take Revlimid.

Take special care with Revlimid
Please talk to your doctor in the following situations:

For women taking Revlimid
Before starting the treatment, you should ask your doctor if you are able to become pregnant, even if you think this is unlikely.

If you are able to become pregnant
- you will have pregnancy tests under the supervision of your doctor (before treatment, every 4 weeks during treatment, and 4 weeks after the treatment has finished) except in the case of confirmed tubal sterilisation AND
- you must use effective methods of contraception for 4 weeks before starting treatment, during treatment, and until 4 weeks after stopping treatment. Your doctor will advise you on appropriate methods of contraception

For men taking Revlimid
It is not known if Revlimid passes into human semen. If your female partner is able to become pregnant, and she doesn't use effective methods of contraception, you must use condoms, during treatment and 1 week after the end of treatment. You should not donate semen during treatment and for 1 week after the end of treatment.

All patients
Before starting the treatment you should tell your doctor if you had blood clots in your veins in the past.
During the treatment with Revlimid you have an increased risk of developing blood clots in the veins.

Before and during the treatment with Revlimid you will have regular blood tests as Revlimid may cause a fall in the blood cells that help fight infection and help the blood to clot. Your doctor should ask you to have a blood test:
- before treatment
- every week for the first 8 weeks of treatment
- at least every month after that.

Your doctor may adjust your dose of Revlimid or stop your treatment based on the results of your blood tests and on your general condition.

Before you start treatment you should tell your doctor if you have kidney disease. Your doctor may adjust your dose of Revlimid based on this information.

You should not donate blood during treatment and for 1 week after the end of treatment.

At the end of the treatment you should return all unused capsules to the pharmacist.

Taking other medicines
Please tell your doctor or pharmacist of all other medicines that you are taking or have recently taken, including medicines obtained without a prescription.

Taking Revlimid with food and drink
The Revlimid capsules can be taken either with or without food (see Section 3, "How and when to take the Revlimid capsule").

Pregnancy
You must not take Revlimid if you are pregnant, as it is expected to be harmful for an unborn baby. In addition, you must not become pregnant while taking Revlimid.
Therefore you must use effective methods of contraception if you are a woman of childbearing potential (see Section 2, "Take special care with Revlimid").

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If you do become pregnant during the treatment with Revlimid, you must stop the treatment and inform your doctor immediately.

For men taking Revlimid, please see section 2 "Take special care with Revlimid". If your partner becomes pregnant whilst you are taking lenalidomide, you should inform your doctor immediately. It is recommended that your partner seeks medical advice.

Breast-feeding
You should not breastfeed when taking Revlimid, as it is not known if Revlimid passes into human milk.

Driving and using machines:
Do not drive or operate machines if you experience side effects, such as dizziness, tiredness, sleepiness or blurred vision.

Important information about some of the ingredients of Revlimid
Revlimid contains lactose (a type of sugar). If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking Revlimid.

3. HOW TO TAKE REVLIMID

Revlimid is taken in combination with dexamethasone. Always take Revlimid and dexamethasone exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. You should refer to the package leaflet for dexamethasone for further information on its use and effects.

Revlimid dosage
The usual starting dose is 25 mg once per day. Revlimid is taken in treatment cycles, each cycle lasting 28 days.

Treatment cycle:
- On days 1-21: take 25 mg of Revlimid once per day
- On days 22-28: do NOT take Revlimid

After completing each cycle, start a new one.

Your doctor may adjust your dose of Revlimid or stop your treatment based on the results of your blood tests and on your general condition (see Section 2, Take special care with Revlimid").

Dexamethasone dosage
The usual starting dose is 40 mg once per day. Dexamethasone is also taken in treatment cycles, each cycle lasting 28 days.

First 4 treatment cycles:
- On days 1-4, 9-12 and 17-20: take 40 mg dexamethasone once per day
- On days 21-28: do NOT take dexamethasone

Following treatment cycles:
- On days 1-4: take 40 mg dexamethasone once per day
- On days 5-28: do NOT take dexamethasone

After completing each cycle, start a new one.

How and when to take Revlimid
You should swallow the Revlimid capsules whole, preferably with water, once a day. Do not break or chew the capsules. The Revlimid capsules can be taken either with or without food.

You should take Revlimid at about the same time each day.

Duration of the treatment with Revlimid
Revlimid is taken in treatment cycles, each cycle lasting 28 days (see above "Dosage"). You should continue the cycles of treatment until your doctor tells you to stop.

If you take more Revlimid than you should
If you take more Revlimid than was prescribed, tell your doctor immediately.

If you forget to take Revlimid
If you forget to take Revlimid at your regular time and
- less than 12 hours have passed: take your capsule immediately.
- more than 12 hours have passed: do not take your capsule. Take your next capsule at the usual time the next day.

If you have any further questions on the use of Revlimid, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Revlimid can cause side effects, although not everybody gets them. The frequency of side effects is classified into the following categories:

Very common	In more than 1 in 10 patients
Common	In more than 1 in 100 patients, but less than 1 in 10
Uncommon	In more than 1 in 1,000 patients, but less than 1 in 100

It is important to note that Revlimid may reduce the number of white blood cells that fight infection and also the blood cells which help the blood to clot (platelets). Revlimid may also cause blood clots in the veins (thrombosis).
Therefore you must tell your doctor immediately if you experience:
- any fever, chills, sore throat, cough, mouth ulcers or any other symptoms of infection
- any bleeding or bruising in the absence of injury
- any chest or leg pain
- any shortness of breath.

Very common side effects are given below. You should consult your doctor if you experience any of these:
- A fall in the number of white blood cells (the cells that fight infection), platelets (the cells that help the blood to clot) and red blood cells (anaemia leading to tiredness and weakness)
- Constipation, diarrhoea, nausea, increase and decrease in weight, rash, sleep disturbance, muscle cramps and muscle weakness, tiredness, swelling of the peripheries.

Common side effects are given below. You should consult your doctor if you experience any of these:
- Infections of all types, fever and flu like symptoms
- Loss of appetite, retention of fluid, dehydration, raised blood sugar levels, changes to the calcium, potassium or magnesium in the blood
- Confusion, seeing or hearing things that do not exist (hallucinations), depression, aggression, agitation, mood changes, anxiety, nervousness, irritability
- Stroke ,paralysis, fainting, memory disturbance, numbness, tingling or burning sensation to the skin, pains in hands or feet, dizziness, headache, tremor, sleepiness, taste disturbance or taste loss, giddiness
- Blurred or reduced vision, cataract, increased tear production
- Leg pain (which could be a symptom of thrombosis), increased blood pressure or a fall in blood pressure especially on standing (which may lead to dizziness or fainting when standing), flushing, chest pain or shortness of breath (which may be a symptom of blood clots in the lungs), irregular heart beat, palpitations

- Cough, hoarseness, hiccoughs
- Vomiting, indigestion, abdominal pain, abdominal swelling, sore inflamed mouth, dry mouth, excessive wind
- Swelling of the face, dry skin, itching, redness of the skin, inflammation of the hair follicles, increased pigmentation of skin, increased sweating, hair loss
- Muscle, bone, back , limb or joint pains or weakness, general feeling of unwellness, generalised swelling
- Production of much more or much less urine than usual (which may be a symptom of kidney failure)
- Difficulty in obtaining an erection, breast enlargement, nipple pain, abnormal menstruation.

Uncommon side effects are given below. You should consult your doctor if you experience any of these:
- Swelling of lymph nodes
- Increased body hair, diabetes, gout, increased appetite, changes to blood chemistry including reduced blood protein (including the proteins that fight infection) and changes to blood phosphate, blood sodium, thyroid hormone and the hormone that controls salt and water absorption, thirst
- Changes to mental status or personality, abnormal dreams, loss of libido, panic attack, restlessness,
- Voice disorder or voice loss, impaired concentration, impaired balance, movement difficulty, loss of sense of smell
- Loss of vision, swelling of eyelid, eye irritation and redness, dry eye , discharge from eye
- Deafness , ear pain or itching, ringing in the ear
- Collapse, circulatory problems, fast, slow or irregular heart beat, shortness of breath especially when lying down (which may be a symptoms of heart failure), bruising
- Wheezing, increased throat secretions, dry throat, nasal or sinus congestion or pain, laryngitis
- Bleeding from bowels, stomach or gums, difficulty or pain on swallowing, haemorrhoids, inflammation, pain or ulceration of mouth, tongue or lips, toothache and coated tongue
- Yellowing of the skin (due to alteration in the function of the liver)
- Skin eruptions, skin cracking, flaking or discoloration, pressure sores, acne, sensitivity to sunlight
- Difficulty passing urine, passing urine more frequently, passing blood in the urine
- Certain types of tumour of skin and brain.

If any of the side effects gets serious, or if you notice any other side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE REVLIMID

- Keep out of the reach and sight of children.
- Do not use Revlimid after the expiry date, which is stated on the blister after "EXP". The expiry date refers to the last day of that month.
- Do not store above 25 C
- Do not use any pack that is damaged or shows signs of tampering.

All unused Revlimid capsules should be returned to the pharmacist.

6. FURTHER INFORMATION

What Revlimid contains

Revlimid 5 mg hard capsules:
- The active substance is lenalidomide. Each capsule contains 5 mg of lenalidomide.

- The other ingredients are:
  - capsule contents: anhydrous lactose, microcrystalline cellulose, croscarmellose sodium and magnesium stearate
  - capsule shell: gelatine and titanium dioxide (E171)
  - printing ink: shellac, propylene glycol, potassium hydroxide and black iron oxide (E172).

Revlimid 10 mg hard capsules:
- The active substance is lenalidomide. Each capsule contains 10 mg of lenalidomide.
- The other ingredients are:
  - capsule contents: anhydrous lactose, microcrystalline cellulose, croscarmellose sodium and magnesium stearate
  - capsule shell: gelatine, titanium dioxide (E171), indigo carmine (E132) and yellow iron oxide (E172)
  - printing ink: shellac, propylene glycol, potassium hydroxide and black iron oxide (E172).

Revlimid 15 mg hard capsules:
- The active substance is lenalidomide. Each capsule contains 15 mg of lenalidomide.
- The other ingredients are:
  - capsule contents: anhydrous lactose, microcrystalline cellulose, croscarmellose sodium and magnesium stearate
  - capsule shell: gelatine, titanium dioxide (E171) and indigo carmine (E132)
  - printing ink: shellac, propylene glycol, potassium hydroxide and black iron oxide (E172).

Revlimid 25 mg hard capsules:
- The active substance is lenalidomide. Each capsule contains 25 mg of lenalidomide.
- The other ingredients are:
  - capsule contents: anhydrous lactose, microcrystalline cellulose, croscarmellose sodium and magnesium stearate
  - capsule shell: gelatine and titanium dioxide (E171)
  - printing ink: shellac, propylene glycol, potassium hydroxide and black iron oxide (E172).

What Revlimid looks like and contents of the pack

Revlimid 5 mg hard capsules are white, with "REV 5 mg" written on them.

Revlimid 10 mg hard capsules are blue-green/pale yellow, with "REV 10 mg" written on them.

Revlimid 15 mg hard capsules are pale blue/white, with "REV 15 mg" written on them.

Revlimid 25 mg hard capsules are white, with "REV 25 mg" written on them.

The capsules are provided in packs. Each pack contains three blisters, each with seven capsules. This gives a total of 21 capsules per pack.

Marketing Authorisation Holder
Celgene Europe Limited
Morgan House
Madeira Walk
Windsor
Berkshire
SL4 1EP
United Kingdom

Manufacturer
Penn Pharmaceutical Services Limited
Tafarnaubach Industrial Estate
Tredegar

Gwent
NP22 3AA
United Kingdom

For any information about this medicine, please contact the Marketing Authorisation Holder.

This leaflet was last approved in {MM/YYYY}

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu/.

ANNEX IV

CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT TO BE IMPLEMENTED BY THE MEMBER STATES

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT TO BE IMPLEMENTED BY THE MEMBER STATES**

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

1. The Member States shall agree the details of a controlled distribution system with the MAH according to national regulations and healthcare system and must implement such programme nationally to ensure that:
   - Prior to launch, all doctors who intend to prescribe Revlimid and all pharmacists who may dispense Revlimid receive a Direct Healthcare Professional Communication as described below.
   - Prior to prescribing (where appropriate, and in agreement with the National Competent Authority, dispensing) all healthcare professionals who intend to prescribe (and dispense) Revlimid are provided with a physician information pack containing the following:
     - Educational Health Care Professional's kit
     - Educational brochures for Patients
     - Patient cards
     - Summary of Product Characteristics (SPC) and Package Leaflet and Labelling.

2. The Member States shall ensure that the MAH implements a pregnancy prevention programme (PPP) within their territory. Details of the PPP should be agreed with the National Competent Authorities in each Member State and put in place prior to the marketing of the product.

3. The Member States should agree the final text of the Direct Healthcare Professional Communication and the physician information pack contents with the MAH and ensure that the materials contain the key elements as described below.

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

5. The Member States should also agree with the MAH prior to the launch of the product:
   - The feasibility of collecting detailed data relating to the indication in order to monitor closely the off-label use within the national territory.
   - The set-up of national measures to assess the effectiveness of and compliance with the PPP

Key elements to be included

Direct Healthcare Professional Communication

The Direct Healthcare Professional Communication shall consist of two parts:
- A core text as agreed by the CHMP.
- National specific requirements agreed with the National Competent Authority regarding:
  - Distribution of the product
  - To ensure that all appropriate measures have been performed prior to Revlimid being dispensed

The Educational Healthcare Professional's Kit

The Educational Health Care Professional's Kit shall contain the following elements:
- Brief background on lenalidomide and its licensed indication
- Posology
- The need to avoid foetal exposure due to teratogenicity of lenalidomide in animals and the expected teratogenic effect of lenalidomide in humans including a summary of the interim results of study CC-5013-TOX-004
- Obligations of the health care professional in relation to the prescribing of Revlimid

- Need to provide comprehensive advice and counselling to patients
- That patients should be capable of complying with the requirements for the safe use of Revlimid
- Need to provide patients with appropriate patient educational brochure and patient card

- Safety advice relevant to all patients
  - Description and management of neutropenia and thrombocytopenia including incidence rates from clinical trials
  - Description and management of thromboembolic risk including incidence rates from clinical trials
  - Use in patients with hepatic and/or renal impairment
  - Disposal of unwanted medicine
  - Local country specific arrangements for a prescription for Revlimid to be dispensed
  - Description of risk of hypothyroidism
  - Explanation of unknown risk of neuropathy with long term use
- Description of the PPP and categorisation of patients based on sex and childbearing potential
  - Algorithm for implementation of PPP
  - Definition of women of childbearing potential (WCBP) and actions the physician should take if unsure
- Safety advice for women of childbearing potential
  - The need to avoid foetal exposure
  - Description of the PPP
  - Need for adequate contraception (even if woman has amenorrhoea) and definition of adequate contraception
  - Pregnancy test regime
    - Advice on suitable tests
    - Before commencing treatment
    - During treatment based on method of contraception
    - After finishing treatment
  - Need to stop Revlimid immediately upon suspicion of pregnancy
  - Need to tell treating doctor immediately upon suspicion of pregnancy
- Safety advice for men
  - The need to avoid foetal exposure
  - The need to use condoms if sexual partner is a WCBP (even if man has had a vasectomy)
    - During Revlimid treatment
    - For one week following final dose.
  - That if his partner becomes pregnant whilst he is taking Revlimid or shortly after he has stopped taking Revlimid he should inform his treating doctor immediately
- Requirements in the event of pregnancy
  - Instructions to stop Revlimid immediately upon suspicion of pregnancy
  - Need to refer to physician specialised or experienced in dealing with teratology and its diagnosis for evaluation and advice
  - Local contact details for reporting of any suspected pregnancy
  - Pregnancy reporting form
- Check list for physicians ensuring that patients receive the appropriate counselling concerning the treatment, contraceptive methods and pregnancy prevention appropriate for their sex and childbearing status
- Adverse event reporting forms

Educatlonal Brochures for patients

The Educational brochures for patients should be of 3 types:
- Brochure for women patients of childbearing potential and their partners
- Brochure for women patients who are not of childbearing potential
- Brochure for male patients

All patient brochures should contain the following elements:
- That lenalidomide is teratogenic in animals and is expected to be teratogenic in humans.
- That Revlimid may cause neutropenia and thrombocytopenia and the need for regular blood tests
- Description of the patient card and its necessity
- Disposal of unwanted medicine
- National or other applicable specific arrangements for a prescription for Revlimid to be dispensed
- That the patient should not give Revlimid to any other person
- That the patient should not donate blood
- That the patient should tell their doctor about any adverse events

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The following information should also be provided in the appropriate brochure:

Brochure for women patients with childbearing potential
- The need to avoid foetal exposure
- Description of the PPP
- Need for adequate contraception and definition of adequate contraception
- Pregnancy test regime
  - Before commencing treatment
  - During treatment every 4 weeks except in case of confirmed tubal sterilisation
  - After finishing treatment
- The need to stop Revlimid immediately upon suspicion of pregnancy
- The need to contact their doctor immediately upon suspicion of pregnancy

Brochure for male patients
- The need to avoid foetal exposure
- The need to use condoms if sexual partner is a WCBP (even if man has had vasectomy)
  - During Revlimid treatment
  - For one week following final dose
- That the patient should not donate semen
- That if his partner becomes pregnant he should inform his treating doctor immediately

Patient Card

The patient card shall contain the following elements:
- Verification that appropriate counselling has taken place
- Documentation of childbearing status potential
- Pregnancy test dates and results