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 opened, 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). Prescribing physicians should carefully evaluate which dose of dexamethasone to use, taking into account the condition and disease status of the patient.

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 1, 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.

No dose adjustments are required for patients with mild renal impairment. The following dose adjustments are recommended at the start of therapy for patients with moderate or severe impaired renal function or end stage renal disease.

Renal Function (CLcr)	Dose Adjustment
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)	5 mg once daily. On dialysis days, the dose should be administered following 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.

** The dose may be escalated to 10 mg once daily if the patient is tolerating the treatment

After initiation of lenalidomide therapy, subsequent lenalidomide dose modification in renally impaired patients should be based on individual patient treatment tolerance, as described above.

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.

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
- 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, pharmacokinetic data has demonstrated that lenalidomide is present in human semen at extremely low levels during treatment and is undetectable in human semen 3 days after stopping the drug in the healthy subject (see section 5.2). As a precaution, all male patients taking lenalidomide must meet the following conditions:
- Understand the expected teratogenic risk if engaged in sexual activity with a pregnant woman or a woman of childbearing potential
- Understand the need for the use of a condom if engaged in sexual activity with a pregnant woman or a woman of childbearing potential.

The prescriber must ensure that for women of childbearing potential:
- The patient complies with the conditions of the 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
Lenalidomide is present in human semen at extremely low levels during treatment and is undetectable in human semen 3 days after stopping the drug in the healthy subject (see section 5.2). As a precaution, and taking into account special populations with prolonged elimination time such as renal impairment, all male patients taking lenalidomide should use condoms throughout treatment duration, during dose interruption and for 1 week after cessation of treatment if their partner is pregnant or 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 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.

Other special warnings and precautions for use

Cardiovascular disorders

Myocardial Infarction
Myocardial infarction has been reported in patients receiving lenalidomide, particularly in those with known risk factors. Patients with known risk factors – including prior thrombosis – should be closely monitored, and action should be taken to try to minimize all modifiable risk factors (eg. smoking, hypertension, and hyperlipidaemia).

Venous and arterial thromboembolic events
In patients with multiple myeloma, the combination of lenalidomide with dexamethasone is associated with an increased risk of venous thromboembolism (predominantly deep vein thrombosis and pulmonary embolism) and arterial thromboembolism (predominantly myocardial infarction and cerebrovascular event) – see sections 4.5 and 4.8.

Consequently, patients with known risk factors for thromboembolism – including prior thrombosis – should be closely monitored. Action should be taken to try to minimize all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia). Concomitant administration of erythropoietic agents or previous history of thromboembolic events 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 12 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 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.

If the patient experiences any thromboembolic events, treatment must be discontinued and standard anticoagulation therapy started. Once the patient has been stabilised on the anticoagulation treatment and any complications of the thromboembolic event have been managed, the lenalidomide treatment may be restarted at the original dose dependent upon a benefit risk assessment. The patient should continue anticoagulation therapy during the course of lenalidomide treatment.

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, especially in case of concomitant medication susceptible to induce bleeding (see Section 4.8 Haemorrhagic disorders). A dose reduction of lenalidomide 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.

Allergic Reactions
Cases of allergic reaction/hypersensitivity reactions have been reported (see section 4.8). Patients who had previous allergic reactions while treated with thalidomide should be monitored closely, as a possible cross-reaction between lenalidomide and thalidomide has been reported in the literature.

Severe skin reactions
Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported. Lenalidomide must be discontinued for exfoliative or bullous rash, or if SJS or TEN is suspected, and should not be resumed following discontinuation for these reactions. Interruption or discontinuation of lenalidomide should be considered for other forms of skin reaction depending on severity. Patients with a history of severe rash associated with thalidomide treatment should not receive lenalidomide.

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.

Second Primary Malignancies

An increase of second primary malignancies (SPM) has been observed in clinical trials in previously treated myeloma patients receiving lenalidomide/dexamethasone (3.98 per 100 patient-years) compared to controls (1.38 per 100 patient-years). Non invasive SPM comprise basal cell or squamous cell skin cancers. Most of the invasive SPMs were solid tumour malignancies.

In clinical trials of newly diagnosed multiple myeloma, a 4-fold increased incidence of second primary malignancies has been observed in patients receiving Revlimid (7.0%) compared with controls (1.8%). Among invasive SPMs, cases of AML, MDS and solid tumours were observed in patients receiving Revlimid in combination with melphalan or immediately following high dose melphalan and ASCT; cases of B-cell malignancies (including Hodgkin's lymphoma) were observed in the clinical trials where patients received Revlimid in the post ASCT setting.

The risk of occurrence of SPM must be taken into account before initiating treatment with Revlimid. Physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of second primary malignancies and institute treatment as indicated.

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. Lenalidomide is not an enzyme inducer. In an *in vitro* study with human hepatocytes, lenalidomide, at various concentrations tested did not induce CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP3A4/5. Therefore, induction leading to reduced efficacy of drugs, including hormonal contraceptives, is not expected if lenalidomide is administered alone. However, 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 Fertility, 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).

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.

Lenalidomide is present in human semen at extremely low levels during treatment and is undetectable in human semen 3 days after stopping the drug in the healthy subject (see section 5.2). As a precaution, and taking into account special populations with prolonged elimination time such as renal impairment, all male patients taking lenalidomide should use condoms throughout treatment duration, during dose interruption and for 1 week after cessation of treatment if their partner is pregnant or 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

a. Summary of the safety profile in patients with multiple myeloma

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 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000 including isolated reports), unknown (cannot be estimated from the available data).

b. Tabulated summary of adverse reactions

The following table is derived from data gathered during the pivotal studies. The data were not adjusted according to the greater duration of treatment in the lenalidomide/dexamethasone versus the placebo/dexamethasone arms in the pivotal studies (See section 5.1).

Table 1: ADRs reported in clinical studies in patients with multiple myeloma treated with lenalidomide

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
Infections and Infestations	**Very Common** Pneumonia, Upper respiratory tract infection **Common** Sepsis, Bacterial, viral and fungal infections (including opportunistic infections), Sinusitis	**Common** Pneumonia, Bacterial, viral and fungal infections (including opportunistic infections)

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
Neoplasms benign, malignant and unspecified	**Uncommon** Basal cell carcinoma Squamous skin cancer^	
Blood and Lymphatic System Disorders	**Very Common** Thrombocytopenia^, Neutropenias^, Anaemia, Haemorrhagic disorder^, Leucopenias **Common** Pancytopenia **Uncommon** Haemolysis, Autoimmune haemolytic anaemia, Haemolytic anaemia	**Very Common** Thrombocytopenia^, Neutropenias^, Leucopenias **Common** Febrile Neutropenia, Anaemia **Uncommon** Hypercoagulation, Coagulopathy
Immune System Disorders	**Uncommon** Hypersensitivity^	
Endocrine Disorders	**Common** Hypothyroidism	
Metabolism and Nutrition Disorders	**Very Common** Hypokalaemia, Decreased appetite **Common** Hypomagnesaemia, Hypocalcaemia, Dehydration	**Common** Hypokalaemia, Hypocalcaemia, Hypophosphataemia
Psychiatric Disorder	**Uncommon** Loss of libido	**Common** Depression
Nervous System disorders	**Very Common** Peripheral neuropathies (excluding motor neuropathy), Dizziness, Tremor, Dysgeusia, Headache **Common** Ataxia, Balance impaired	**Common** Cerebrovascular Accident, Dizziness, Syncope **Uncommon** Intracranial haemorrhage^, Transient ischaemic attack, Cerebral ischaemia
Eye Disorders	**Very Common** Blurred vision **Common** Reduced visual acuity, Cataract	**Common** Cataract **Uncommon** Blindness
Ear and Labyrinth Disorders	**Common** Deafness (Including Hypoacusis), Tinnitus	
Cardiac Disorders	**Common** Atrial Fibrillation, Bradycardia **Uncommon** Arrhythmia, QT prolongation, Atrial flutter, Ventricular extrasystoles	**Common** Myocardial infarction^, Atrial Fibrillation, Congestive Cardiac, Failure, Tachycardia
Vascular Disorders	**Very Common** Venous Thromboembolic Events, predominantly Deep Vein Thrombosis and Pulmonary Embolism^ **Common** Hypotension, Hypertension, Ecchymosis^	**Very Common** Venous Thromboembolic Events, predominantly Deep Vein Thrombosis and Pulmonary Embolism^ **Uncommon** Ischemia, Peripheral ischemia, Intracranial venous sinus thrombosis

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
Respiratory, Thoracic and Mediastinal Disorders	**Very common** Dyspnoea, Nasopharyngitis, Pharyngitis, Bronchitis, Epistaxis^	**Common** Respiratory Distress
Gastrointestinal Disorders	**Very Common** Constipation, Diarrhoea, Nausea, Vomiting **Common** Gastrointestinal Haemorrhage (including rectal haemorrhage, haemorrhoidal haemorrhage, peptic ulcer haemorrhage and gingival bleeding)^, Abdominal Pain, Dry Mouth, Stomatitis, Dysphagia **Uncommon** Colitis, Caecitis	**Common** Diarrhoea, Constipation, Nausea
Hepatobiliary Disorders	**Common** Abnormal Liver Function Tests	**Common** Abnormal Liver Function Tests
Skin and Subcutaneous tissue Disorders	**Very Common** Rashes **Common** Urticaria, Hyperhidrosis, Dry Skin, Pruritus, Skin Hyperpigmentation, Eczema **Uncommon** Skin discolouration, Photosensitivity reaction	**Common** Rashes
Musculoskeletal and connective tissue disorders	**Very Common** Muscle Spasms, Bone Pain, Musculoskeletal and connective tissue pain and discomfort **Common** Joint swelling	**Common** Muscle Weakness, Bone Pain **Uncommon** Joint swelling
Renal and Urinary Disorders	**Common** Haematuria^, Urinary retention , Urinary incontinence **Uncommon** Acquired Fanconi syndrome	**Common** Renal failure **Uncommon** Renal tubular necrosis
Reproductive System and Breast Disorders	**Common** Erectile Dysfunction	
General disorders and administration site conditions	**Very Common** Fatigue, Oedema (including peripheral oedema), Pyrexia, Influenza like illness syndrome (including pyrexia, myalgia, musculoskeletal pain, headache and rigors) **Common** Chest Pain, Lethargy	**Common** Fatigue
Injury, poisoning and procedural complications	**Common** Contusion^	

^See section 4.8c.

In addition to the above adverse drug reactions identified from the pivotal trials, the following table is derived from data gathered during post-marketing experience.

Table 2: Summary of adverse drug reactions identified from post-marketing data in patients treated with lenalidomide

System organ class	Reactions/frequency
Neoplasms benign, malignant and unspecified	Rare: Tumour lysis syndrome
Respiratory, Thoracic and Mediastinal Disorders	Unknown: Interstitial pneumonitis
Gastrointestinal disorders	Unknown: Pancreatitis
Skin and subcutaneous system disorders	Uncommon: Angioedema Rare: Stevens-Johnson Syndrome^, toxic epidermal necrolysis^

^see section 4.8c

c. Description of selected adverse reactions

Teratogenicity
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.

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). Grade 4 febrile neutropenia episodes were observed infrequently (0.6% in lenalidomide/dexamethasone-treated patients compared to 0.0% in placebo/dexamethasone treated patients).

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).

Venous thromboembolism
The combination of lenalidomide with dexamethasone is associated with an increased risk of DVT and PE in patients with multiple myeloma (see section 4.5). Concomitant administration of erythropoietic agents or previous history of DVT may also increase thrombotic risk in these patients.

Myocardial Infarction
Myocardial infarction has been reported in patients receiving lenalidomide, particularly in those with known risk factors.

Haemorrhagic disorders
Haemorrhagic disorders are listed under several system organ classes: Blood and lymphatic system disorders; nervous system disorders (intracranial haemorrhage); respiratory, thoracic and mediastinal disorders (epistaxis); gastrointestinal disorders (gingival bleeding, haemorrhoidal haemorrhage, rectal haemorrhage); renal and urinary disorders (haematuria); Injury, poisoning and procedural complications (contusion) and vascular disorders (ecchymosis).

Allergic Reactions
Cases of allergic reaction/hypersensitivity reactions have been reported. A possible cross-reaction between lenalidomide and thalidomide has been reported in the literature.

Severe skin reactions
Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported. Patients with a history of severe rash associated with thalidomide treatment should not receive lenalidomide.

Second Primary Malignancies
*In clinical trials in previously treated myeloma patients with Lenalidomide/Dexamethasone compared to controls, mainly comprising of basal cell or squamous cell skin cancers.

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 150 mg, and in single-dose studies, some patients were exposed to up to 400 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 (median follow-up duration of 98.0 weeks). Complete response and overall response 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.

An extended follow-up efficacy analysis was conducted with a median follow-up of 130.7 weeks. Table 1 summarises the results of the follow-up efficacy analyses – pooled studies MM-009 and MM-010.

In this pooled extended follow-up analysis, the median TTP was 60.1 weeks (95% CI: 44.3, 73.1) in patients treated with lenalidomide/dexamethasone (N = 353) versus 20.1 weeks (95% CI: 17.7, 20.3) in patients treated with placebo/dexamethasone (N = 351). The median progression free survival was 48.1 weeks (95% CI: 36.4, 62.1) in patients treated with lenalidomide/dexamethasone versus 20.0 weeks (95% CI: 16.1, 20.1) in patients treated with placebo/dexamethasone. The median duration of treatment was 44.0 weeks (min: 0.1, max: 254.9) for lenalidomide/dexamethasone and 23.1 weeks (min: 0.3, max: 238.1) for placebo/dexamethasone. Complete response (CR), partial response (PR) and overall response (CR+PR) rates in the lenalidomide/dexamethasone arm remain significantly higher than in the dexamethasone/placebo arm in both studies. The median overall survival in the extended follow-up analysis of the pooled studies is 164.3 weeks (95% CI: 145.1, 192.6) in patients treated with lenalidomide/dexamethasone versus 136.4 weeks (95% CI: 113.1, 161.7) in patients treated with placebo/dexamethasone. Despite the fact that 170 out of the 351 patients randomised to placebo/dexamethasone received lenalidomide after disease progression or after the studies were unblinded, the pooled analysis of overall survival demonstrated a statistically significant survival advantage for lenalidomide/dexamethasone relative to placebo/dexamethasone (hazard ratio = 0.833, 95% CI = [0.687, 1.009], p=0.045).

Table 1: Summary of Results of Efficacy Analyses as of cut-off date for extended follow-up — Pooled Studies MM-009 and MM-010 (cut-offs 23 July 2008 and 2 March 2008, respectively)

Endpoint	**len/dex (N=353)**	**placebo/dex (N=351)**	
Time to Event			**Hazard ratio [95% CI], p-value** [a]
Time To Progression Median [95% CI], weeks	60.1 [44.3, 73.1]	20.1 [17.7, 20.3]	0.350 [0. 287, 0. 426] , p < 0.001
Progression Free Survival Median [95% CI], weeks	48.1 [36. 4, 62.1]	20.0 [16.1, 20.1]	0.393 [0.326, 0.473] p < 0.001
Overall Survival Median [95% CI], weeks 1-year Overall Survival rate	164.3 [145.1, 192.6] 82%	136.4 [113.1, 161.7] 75%	0.833 [0.687, , 1.009] p = 0.045
Response rate			**Odds ratio [95% CI], p-value** [b]
Overall Response [n, %] Complete Response [n, %]	212 (60.1) 58 (16.4)	75 (21.4) 11 (3.1)	5.53 [3.97, 7.71], p < 0.001 6.08 [3.13, 11.80], p < 0.001

a: Two-tailed log rank test comparing survival curves between treatment groups.
b: Two-tailed continuity-corrected chi-square test.

Exploratory study

An open-label, randomized, multicenter, Phase 3 study was conducted in 445 patients with newly diagnosed multiple myeloma; 222 patients were randomized to the lenalidomide/low dose dexamethasone arm, and 223 were randomized to the lenalidomide/standard dose dexamethasone arm.

Patients randomized to the lenalidomide/standard dose dexamethasone arm received lenalidomide 25 mg/day, Days 1 to 21 every 28 days plus dexamethasone 40 mg/day on Days 1 to 4, 9 to 12, and 17 to 20 every 28 days for the first four cycles. Patients randomized to the lenalidomide/low dose dexamethasone arm received lenalidomide 25 mg/day, Days 1 to 21 every 28 days plus low dose dexamethasone – 40 mg/day on Days 1, 8, 15, and 22 every 28 days. In the lenalidomide/low dose dexamethasone group, 20 patients (9.1%) underwent at least one dose interruption compared to 65 patients (29.3%) in the lenalidomide/standard dose dexamethasone arm.

In a post-hoc analysis, lower mortality was observed in the lenalidomide/low dose dexamethasone arm 6.8% (15/220) compared to the lenalidomide/standard dose dexamethasone arm 19.3% (43/223), in the newly diagnosed multiple myeloma patient population, with a median follow up of 72.3 weeks.

However with a longer follow-up, the difference in overall survival in favour of low dose dexamethasone tends to decrease.

Considering that the patient population differs from the authorised indication, these results should be interpreted with caution.

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 is rapidly absorbed following oral administration in healthy volunteers, under fasting conditions, with maximum plasma concentrations occurring between 0.5 and 2 hours post-dose. In patients, as well as in healthy volunteers, the maximum concentration (C_{max}) and area-under-the-concentration time curve (AUC) increase proportionally 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.

Co-administration with a high-fat and high-calorie meal in healthy volunteers reduces the extent of absorption, resulting in an approximately 20% decrease in area under the concentration versus time curve (AUC) and 50% decrease in Cmax in plasma. However, in the pivotal multiple myeloma registration trials where the efficacy and safety were established for lenalidomide, the drug was administered without regard to food intake. Thus, lenalidomide can be administered with or without food.

Distribution
In vitro (^{14}C)-lenalidomide binding to plasma proteins was low with mean plasma protein binding at 23% and 29% in multiple myeloma patients and healthy volunteers, respectively.

Lenalidomide is present in human semen (< 0.01% of the dose) after administration of 25 mg/day and the drug is undetectable in semen of a healthy subject 3 days after stopping the drug (see section 4.4).

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 through urinary excretion. The contribution of renal excretion to total clearance in subjects with normal renal function was 90%, with 4% of lenalidomide eliminated in faeces.

Lenalidomide is poorly metabolized as 82% of the dose is excreted unchanged in urine. Hydroxy-lenalidomide and N-acetyl-lenalidomide represent 4.59% and 1.83% of the excreted dose,

respectively. The renal clearance of lenalidomide exceeds the glomerular filtration rate and therefore is at least actively secreted to some extent.
At recommended doses (5 to 25 mg/day), half-life in plasma is approximately 3 hours in healthy volunteers and patients with multiple myeloma.

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.

5.3 Preclinical safety data

An embryofoetal development study has been conducted in monkeys administered lenalidomide at doses from 0.5 and up to 4 mg/kg/day. Findings from this study indicate that lenalidomide produced external malformations including non-patent anus and malformations of upper and lower extremities (bent, shortened, malformed, malrotated and/or absent part of the extremities, oligo and/or polydactyly) in the offspring of female monkeys who received the drug during pregnancy.

Various visceral effects (discoloration, red foci at different organs, small colorless mass above atrio-ventricular valve, small gall bladder, malformed diaphragm) were also observed in single fetuses.

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 comparisons.

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

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
1 Longwalk Road
Stockley Park
Uxbridge
UB11 1DB
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 website of the European Medicines Agency: http://www.ema.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 opened, 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). Prescribing physicians should carefully evaluate which dose of dexamethasone to use, taking into account the condition and disease status of the patient.

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 1, 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.

No dose adjustments are required for patients with mild renal impairment. The following dose adjustments are recommended at the start of therapy for patients with moderate or severe impaired renal function or end stage renal disease.

Renal Function (CLcr)	Dose Adjustment
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)	5 mg once daily. On dialysis days, the dose should be administered following 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.

** The dose may be escalated to 10 mg once daily if the patient is tolerating the treatment

After initiation of lenalidomide therapy, subsequent lenalidomide dose modification in renally impaired patients should be based on individual patient treatment tolerance, as described above.

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.

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
- 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, pharmacokinetic data has demonstrated that lenalidomide is present in human semen at extremely low levels during treatment and is undetectable in human semen 3 days after stopping the drug in the healthy subject (see section 5.2). As a precaution, all male patients taking lenalidomide must meet the following conditions:
- Understand the expected teratogenic risk if engaged in sexual activity with a pregnant woman or a woman of childbearing potential
- Understand the need for the use of a condom if engaged in sexual activity with a pregnant woman or a woman of childbearing potential.

The prescriber must ensure that for women of childbearing potential:
- The patient complies with the conditions of the 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
Lenalidomide is present in human semen at extremely low levels during treatment and is undetectable in human semen 3 days after stopping the drug in the healthy subject (see section 5.2). As a precaution, and taking into account special populations with prolonged elimination time such as renal impairment, all male patients taking lenalidomide should use condoms throughout treatment duration, during dose interruption and for 1 week after cessation of treatment if their partner is pregnant or 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 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.

Other special warnings and precautions for use

Cardiovascular disorders

Myocardial Infarction
Myocardial infarction has been reported in patients receiving lenalidomide, particularly in those with known risk factors. Patients with known risk factors – including prior thrombosis – should be closely monitored, and action should be taken to try to minimize all modifiable risk factors (eg. smoking, hypertension, and hyperlipidaemia).

Venous and arterial thromboembolic events
In patients with multiple myeloma, the combination of lenalidomide with dexamethasone is associated with an increased risk of venous thromboembolism (predominantly deep vein thrombosis and pulmonary embolism) and arterial thromboembolism (predominantly myocardial infarction and cerebrovascular event) – see sections 4.5 and 4.8.

Consequently, patients with known risk factors for thromboembolism – including prior thrombosis – should be closely monitored. Action should be taken to try to minimize all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia). Concomitant administration of erythropoietic agents or previous history of thromboembolic events 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 12 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 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.

If the patient experiences any thromboembolic events, treatment must be discontinued and standard anticoagulation therapy started. Once the patient has been stabilised on the anticoagulation treatment and any complications of the thromboembolic event have been managed, the lenalidomide treatment may be restarted at the original dose dependent upon a benefit risk assessment. The patient should continue anticoagulation therapy during the course of lenalidomide treatment.

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, especially in case of concomitant medication susceptible to induce bleeding (see Section 4.8 Haemorrhagic disorders). A dose reduction of lenalidomide 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.

Allergic Reactions
Cases of allergic reaction/hypersensitivity reactions have been reported (see section 4.8). Patients who had previous allergic reactions while treated with thalidomide should be monitored closely, as a possible cross-reaction between lenalidomide and thalidomide has been reported in the literature.

Severe skin reactions
Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported. Lenalidomide must be discontinued for exfoliative or bullous rash, or if SJS or TEN is suspected, and should not be resumed following discontinuation for these reactions. Interruption or discontinuation of lenalidomide should be considered for other forms of skin reaction depending on severity. Patients with a history of severe rash associated with thalidomide treatment should not receive lenalidomide.

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.

Second Primary Malignancies

An increase of second primary malignancies (SPM) has been observed in clinical trials in previously treated myeloma patients receiving lenalidomide/dexamethasone (3.98 per 100 patient-years) compared to controls (1.38 per 100 patient-years). Non invasive SPM comprise basal cell or squamous cell skin cancers. Most of the invasive SPMs were solid tumour malignancies.

In clinical trials of newly diagnosed multiple myeloma, a 4-fold increased incidence of second primary malignancies has been observed in patients receiving Revlimid (7.0%) compared with controls (1.8%). Among invasive SPMs, cases of AML, MDS and solid tumours were observed in patients receiving Revlimid in combination with melphalan or immediately following high dose melphalan and ASCT; cases of B-cell malignancies (including Hodgkin's lymphoma) were observed in the clinical trials where patients received Revlimid in the post ASCT setting.

The risk of occurrence of SPM must be taken into account before initiating treatment with Revlimid. Physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of second primary malignancies and institute treatment as indicated.

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. Lenalidomide is not an enzyme inducer. In an *in vitro* study with human hepatocytes, lenalidomide, at various concentrations tested did not induce CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP3A4/5. Therefore, induction leading to reduced efficacy of drugs, including hormonal contraceptives, is not expected if lenalidomide is administered alone. However, 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 Fertility, 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).

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.

Lenalidomide is present in human semen at extremely low levels during treatment and is undetectable in human semen 3 days after stopping the drug in the healthy subject (see section 5.2). As a precaution, and taking into account special populations with prolonged elimination time such as renal impairment, all male patients taking lenalidomide should use condoms throughout treatment duration, during dose interruption and for 1 week after cessation of treatment if their partner is pregnant or 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

a. Summary of the safety profile in patients with multiple myeloma

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 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000 including isolated reports), unknown (cannot be estimated from the available data).

b. Tabulated summary of adverse reactions

The following table is derived from data gathered during the pivotal studies. The data were not adjusted according to the greater duration of treatment in the lenalidomide/dexamethasone versus the placebo/dexamethasone arms in the pivotal studies (See section 5.1).

Table 1: ADRs reported in clinical studies in patients with multiple myeloma treated with lenalidomide

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
Infections and Infestations	**Very Common** Pneumonia, Upper respiratory tract infection **Common** Sepsis, Bacterial, viral and fungal infections (including opportunistic infections), Sinusitis	**Common** Pneumonia, Bacterial, viral and fungal infections (including opportunistic infections)
Neoplasms benign, malignant and unspecified	**Uncommon** Basal cell carcinoma Squamous skin cancer^	
Blood and Lymphatic System Disorders	**Very Common** Thrombocytopenia^, Neutropenias^, Anaemia, Haemorrhagic disorder^, Leucopenias **Common** Pancytopenia **Uncommon** Haemolysis, Autoimmune haemolytic anaemia, Haemolytic anaemia	**Very Common** Thrombocytopenia^, Neutropenias^, Leucopenias **Common** Febrile Neutropenia, Anaemia **Uncommon** Hypercoagulation, Coagulopathy
Immune System Disorders	**Uncommon** Hypersensitivity^	
Endocrine Disorders	**Common** Hypothyroidism	

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
Metabolism and Nutrition Disorders	**Very Common** Hypokalaemia, Decreased appetite **Common** Hypomagnesaemia, Hypocalcaemia, Dehydration	**Common** Hypokalaemia, Hypocalcaemia, Hypophosphataemia
Psychiatric Disorder	**Uncommon** Loss of libido	**Common** Depression
Nervous System disorders	**Very Common** Peripheral neuropathies (excluding motor neuropathy), Dizziness, Tremor, Dysgeusia, Headache **Common** Ataxia, Balance impaired	**Common** Cerebrovascular Accident, Dizziness, Syncope **Uncommon** Intracranial haemorrhage^, Transient ischaemic attack, Cerebral ischaemia
Eye Disorders	**Very Common** Blurred vision **Common** Reduced visual acuity, Cataract	**Common** Cataract **Uncommon** Blindness
Ear and Labyrinth Disorders	**Common** Deafness (Including Hypoacusis), Tinnitus	
Cardiac Disorders	**Common** Atrial Fibrillation, Bradycardia **Uncommon** Arrhythmia, QT prolongation, Atrial flutter, Ventricular extrasystoles	**Common** Myocardial infarction^, Atrial Fibrillation, Congestive Cardiac, Failure, Tachycardia
Vascular Disorders	**Very Common** Venous Thromboembolic Events, predominantly Deep Vein Thrombosis and Pulmonary Embolism^ **Common** Hypotension, Hypertension, Ecchymosis^	**Very Common** Venous Thromboembolic Events, predominantly Deep Vein Thrombosis and Pulmonary Embolism^ **Uncommon** Ischemia, Peripheral ischemia, Intracranial venous sinus thrombosis
Respiratory, Thoracic and Mediastinal Disorders	**Very common** Dyspnoea, Nasopharyngitis, Pharyngitis, Bronchitis, Epistaxis^	**Common** Respiratory Distress
Gastrointestinal Disorders	**Very Common** Constipation, Diarrhoea, Nausea, Vomiting **Common** Gastrointestinal Haemorrhage (including rectal haemorrhage, haemorrhoidal haemorrhage, peptic ulcer haemorrhage and gingival bleeding)^, Abdominal Pain, Dry Mouth, Stomatitis, Dysphagia **Uncommon** Colitis, Caecitis	**Common** Diarrhoea, Constipation, Nausea
Hepatobiliary Disorders	**Common** Abnormal Liver Function Tests	**Common** Abnormal Liver Function Tests

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
Skin and Subcutaneous tissue Disorders	**Very Common** Rashes **Common** Urticaria, Hyperhidrosis, Dry Skin, Pruritus, Skin Hyperpigmentation, Eczema **Uncommon** Skin discolouration, Photosensitivity reaction	**Common** Rashes
Musculoskeletal and connective tissue disorders	**Very Common** Muscle Spasms, Bone Pain, Musculoskeletal and connective tissue pain and discomfort **Common** Joint swelling	**Common** Muscle Weakness, Bone Pain **Uncommon** Joint swelling
Renal and Urinary Disorders	**Common** Haematuria^, Urinary retention , Urinary incontinence **Uncommon** Acquired Fanconi syndrome	**Common** Renal failure **Uncommon** Renal tubular necrosis
Reproductive System and Breast Disorders	**Common** Erectile Dysfunction	
General disorders and administration site conditions	**Very Common** Fatigue, Oedema (including peripheral oedema), Pyrexia, Influenza like illness syndrome (including pyrexia, myalgia, musculoskeletal pain, headache and rigors) **Common** Chest Pain, Lethargy	**Common** Fatigue
Injury, poisoning and procedural complications	**Common** Contusion^	

^See section 4.8c.

In addition to the above adverse drug reactions identified from the pivotal trials, the following table is derived from data gathered during post-marketing experience.

Table 2: Summary of adverse drug reactions identified from post-marketing data in patients treated with lenalidomide

System organ class	Reactions/frequency
Neoplasms benign, malignant and unspecified	Rare: Tumour lysis syndrome
Respiratory, Thoracic and Mediastinal Disorders	Unknown: Interstitial pneumonitis
Gastrointestinal disorders	Unknown: Pancreatitis
Skin and subcutaneous system disorders	Uncommon: Angioedema Rare: Stevens-Johnson Syndrome^, toxic epidermal necrolysis^

^see section 4.8c

c. Description of selected adverse reactions

Teratogenicity
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.

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). Grade 4 febrile neutropenia episodes were observed infrequently (0.6% in lenalidomide/dexamethasone-treated patients compared to 0.0% in placebo/dexamethasone treated patients).

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).

Venous thromboembolism
The combination of lenalidomide with dexamethasone is associated with an increased risk of DVT and PE in patients with multiple myeloma (see section 4.5). Concomitant administration of erythropoietic agents or previous history of DVT may also increase thrombotic risk in these patients.

Myocardial Infarction
Myocardial infarction has been reported in patients receiving lenalidomide, particularly in those with known risk factors.

Haemorrhagic disorders
Haemorrhagic disorders are listed under several system organ classes: Blood and lymphatic system disorders; nervous system disorders (intracranial haemorrhage); respiratory, thoracic and mediastinal disorders (epistaxis); gastrointestinal disorders (gingival bleeding, haemorrhoidal haemorrhage, rectal haemorrhage); renal and urinary disorders (haematuria); Injury, poisoning and procedural complications (contusion) and vascular disorders (ecchymosis).

Allergic Reactions
Cases of allergic reaction/hypersensitivity reactions have been reported. A possible cross-reaction between lenalidomide and thalidomide has been reported in the literature.

Severe skin reactions
Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported. Patients with a history of severe rash associated with thalidomide treatment should not receive lenalidomide.

Second Primary Malignancies
*In clinical trials in previously treated myeloma patients with Lenalidomide/Dexamethasone compared to controls, mainly comprising of basal cell or squamous cell skin cancers.

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 150 mg, and in single-dose studies, some patients were exposed to up to 400 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 (median follow-up duration of 98.0 weeks). Complete response and overall response 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.

An extended follow-up efficacy analysis was conducted with a median follow-up of 130.7 weeks. Table 1 summarises the results of the follow-up efficacy analyses – pooled studies MM-009 and MM-010.

In this pooled extended follow-up analysis, the median TTP was 60.1 weeks (95% CI: 44.3, 73.1) in patients treated with lenalidomide/dexamethasone (N = 353) versus 20.1 weeks (95% CI: 17.7, 20.3) in patients treated with placebo/dexamethasone (N = 351). The median progression free survival was 48.1 weeks (95% CI: 36.4, 62.1) in patients treated with lenalidomide/dexamethasone versus 20.0 weeks (95% CI: 16.1, 20.1) in patients treated with placebo/dexamethasone. The median duration of treatment was 44.0 weeks (min: 0.1, max: 254.9) for lenalidomide/dexamethasone and 23.1 weeks (min: 0.3, max: 238.1) for placebo/dexamethasone. Complete response (CR), partial response (PR) and overall response (CR+PR) rates in the lenalidomide/dexamethasone arm remain significantly

higher than in the dexamethasone/placebo arm in both studies. The median overall survival in the extended follow-up analysis of the pooled studies is 164.3 weeks (95% CI: 145.1, 192.6) in patients treated with lenalidomide/dexamethasone versus 136.4 weeks (95% CI: 113.1, 161.7) in patients treated with placebo/dexamethasone. Despite the fact that 170 out of the 351 patients randomised to placebo/dexamethasone received lenalidomide after disease progression or after the studies were unblinded, the pooled analysis of overall survival demonstrated a statistically significant survival advantage for lenalidomide/dexamethasone relative to placebo/dexamethasone (hazard ratio = 0.833, 95% CI = [0.687, 1.009], p=0.045).

Table 1: Summary of Results of Efficacy Analyses as of cut-off date for extended follow-up — Pooled Studies MM-009 and MM-010 (cut-offs 23 July 2008 and 2 March 2008, respectively)

Endpoint	**len/dex (N=353)**	**placebo/dex(N =351)**	
Time to Event			**Hazard ratio [95% CI], p-value** [a]
Time To Progression Median [95% CI], weeks	60.1 [44.3, 73.1]	20.1 [17.7, 20.3]	0.350 [0.287, 0.426], p < 0.001
Progression Free Survival Median [95% CI], weeks	48.1 [36.4, 62.1]	20.0 [16.1, 20.1]	0.393 [0.326, 0.473] p < 0.001 [b]
Overall Survival Median [95% CI], weeks 1-year Overall Survival rate	164.3 [145.1, 192.6] 82%	136.4 [113.1, 161.7] 75%	0.833 [0. 687, 1.009] p = 0.045
Response rate			**Odds ratio [95% CI], p-value** [b]
Overall Response [n, %] Complete Response [n, %]	212 (60.1) 58 (16.4)	75 (21.4) 11 (3.1)	5.53 [3.97, 7.71], p < 0.001 6.08 [3.13, 11.80], p < 0.001

a: Two-tailed log rank test comparing survival curves between treatment groups.
b: Two-tailed continuity-corrected chi-square test.

Exploratory study

An open-label, randomized, multicenter, Phase 3 study was conducted in 445 patients with newly diagnosed multiple myeloma; 222 patients were randomized to the lenalidomide/low dose dexamethasone arm, and 223 were randomized to the lenalidomide/standard dose dexamethasone arm. Patients randomized to the lenalidomide/standard dose dexamethasone arm received lenalidomide 25 mg/day, Days 1 to 21 every 28 days plus dexamethasone 40 mg/day on Days 1 to 4, 9 to 12, and 17 to 20 every 28 days for the first four cycles. Patients randomized to the lenalidomide/low dose dexamethasone arm received lenalidomide 25 mg/day, Days 1 to 21 every 28 days plus low dose dexamethasone – 40 mg/day on Days 1, 8, 15, and 22 every 28 days. In the lenalidomide/low dose dexamethasone group, 20 patients (9.1%) underwent at least one dose interruption compared to 65 patients (29.3%) in the lenalidomide/standard dose dexamethasone arm.

In a post-hoc analysis, lower mortality was observed in the lenalidomide/low dose dexamethasone arm 6.8% (15/220) compared to the lenalidomide/standard dose dexamethasone arm 19.3% (43/223), in the newly diagnosed multiple myeloma patient population, with a median follow up of 72.3 weeks.

However with a longer follow-up, the difference in overall survival in favour of low dose dexamethasone tends to decrease.

Considering that the patient population differs from the authorised indication, these results should be interpreted with caution.

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 is rapidly absorbed following oral administration in healthy volunteers, under fasting conditions, with maximum plasma concentrations occurring between 0.5 and 2 hours post-dose. In patients, as well as in healthy volunteers, the maximum concentration (C_{max}) and area-under-the-concentration time curve (AUC) increase proportionally 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.

Co-administration with a high-fat and high-calorie meal in healthy volunteers reduces the extent of absorption, resulting in an approximately 20% decrease in area under the concentration versus time curve (AUC) and 50% decrease in Cmax in plasma. However, in the pivotal multiple myeloma registration trials where the efficacy and safety were established for lenalidomide, the drug was administered without regard to food intake. Thus, lenalidomide can be administered with or without food.

Distribution
In vitro (^{14}C)-lenalidomide binding to plasma proteins was low with mean plasma protein binding at 23% and 29% in multiple myeloma patients and healthy volunteers, respectively.

Lenalidomide is present in human semen (< 0.01% of the dose) after administration of 25 mg/day and the drug is undetectable in semen of a healthy subject 3 days after stopping the drug (see section 4.4).

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 through urinary excretion. The contribution of renal excretion to total clearance in subjects with normal renal function was 90%, with 4% of lenalidomide eliminated in faeces.

Lenalidomide is poorly metabolized as 82% of the dose is excreted unchanged in urine. Hydroxy-lenalidomide and N-acetyl-lenalidomide represent 4.59% and 1.83% of the excreted dose, respectively. The renal clearance of lenalidomide exceeds the glomerular filtration rate and therefore is at least actively secreted to some extent.
At recommended doses (5 to 25 mg/day), half-life in plasma is approximately 3 hours in healthy volunteers and patients with multiple myeloma.

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.

5.3 Preclinical safety data

An embryofoetal development study has been conducted in monkeys administered lenalidomide at doses from 0.5 and up to 4 mg/kg/day. Findings from this study indicate that lenalidomide produced external malformations including non-patent anus and malformations of upper and lower extremities

(bent, shortened, malformed, malrotated and/or absent part of the extremities, oligo and/or polydactyly) in the offspring of female monkeys who received the drug during pregnancy.

Various visceral effects (discoloration, red foci at different organs, small colorless mass above atrio-ventricular valve, small gall bladder, malformed diaphragm) were also observed in single fetuses.

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 comparisons.

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

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

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
1 Longwalk Road
Stockley Park
Uxbridge
UB11 1DB
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 website of the European Medicines Agency: http://www.ema.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 opened, 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). Prescribing physicians should carefully evaluate which dose of dexamethasone to use, taking into account the condition and disease status of the patient.

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 1, 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.

No dose adjustments are required for patients with mild renal impairment. The following dose adjustments are recommended at the start of therapy for patients with moderate or severe impaired renal function or end stage renal disease.

Renal Function (CLcr)	Dose Adjustment
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)	5 mg once daily. On dialysis days, the dose should be administered following 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.

** The dose may be escalated to 10 mg once daily if the patient is tolerating the treatment

After initiation of lenalidomide therapy, subsequent lenalidomide dose modification in renally impaired patients should be based on individual patient treatment tolerance, as described above.

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.

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
- 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, pharmacokinetic data has demonstrated that lenalidomide is present in human semen at extremely low levels during treatment and is undetectable in human semen 3 days after stopping the drug in the healthy subject (see section 5.2). As a precaution, all male patients taking lenalidomide must meet the following conditions:
- Understand the expected teratogenic risk if engaged in sexual activity with a pregnant woman or a woman of childbearing potential
- Understand the need for the use of a condom if engaged in sexual activity with a pregnant woman or a woman of childbearing potential.

The prescriber must ensure that for women of childbearing potential:
- The patient complies with the conditions of the 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
Lenalidomide is present in human semen at extremely low levels during treatment and is undetectable in human semen 3 days after stopping the drug in the healthy subject (see section 5.2). As a precaution, and taking into account special populations with prolonged elimination time such as renal impairment, all male patients taking lenalidomide should use condoms throughout treatment duration, during dose interruption and for 1 week after cessation of treatment if their partner is pregnant or 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 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.

Other special warnings and precautions for use

Cardiovascular disorders

Myocardial Infarction
Myocardial infarction has been reported in patients receiving lenalidomide, particularly in those with known risk factors. Patients with known risk factors – including prior thrombosis – should be closely monitored, and action should be taken to try to minimize all modifiable risk factors (eg. smoking, hypertension, and hyperlipidaemia).

Venous and arterial thromboembolic events
In patients with multiple myeloma, the combination of lenalidomide with dexamethasone is associated with an increased risk of venous thromboembolism (predominantly deep vein thrombosis and pulmonary embolism) and arterial thromboembolism (predominantly myocardial infarction and cerebrovascular event) – see sections 4.5 and 4.8.

Consequently, patients with known risk factors for thromboembolism – including prior thrombosis – should be closely monitored. Action should be taken to try to minimize all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia). Concomitant administration of erythropoietic agents or previous history of thromboembolic events 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 12 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 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.

If the patient experiences any thromboembolic events, treatment must be discontinued and standard anticoagulation therapy started. Once the patient has been stabilised on the anticoagulation treatment and any complications of the thromboembolic event have been managed, the lenalidomide treatment may be restarted at the original dose dependent upon a benefit risk assessment. The patient should continue anticoagulation therapy during the course of lenalidomide treatment.

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, especially in case of concomitant medication susceptible to induce bleeding (see Section 4.8 Haemorrhagic disorders). A dose reduction of lenalidomide 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.

Allergic Reactions
Cases of allergic reaction/hypersensitivity reactions have been reported (see section 4.8). Patients who had previous allergic reactions while treated with thalidomide should be monitored closely, as a possible cross-reaction between lenalidomide and thalidomide has been reported in the literature.

Severe skin reactions
Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported. Lenalidomide must be discontinued for exfoliative or bullous rash, or if SJS or TEN is suspected, and should not be resumed following discontinuation for these reactions. Interruption or discontinuation of lenalidomide should be considered for other forms of skin reaction depending on severity. Patients with a history of severe rash associated with thalidomide treatment should not receive lenalidomide.

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.

Second Primary Malignancies

An increase of second primary malignancies (SPM) has been observed in clinical trials in previously treated myeloma patients receiving lenalidomide/dexamethasone (3.98 per 100 patient-years) compared to controls (1.38 per 100 patient-years). The majority of SPMs were non invasive SPM which comprise basal cell or squamous cell skin cancers. Most of the invasive SPMs were solid tumour malignancies.

In clinical trials of newly diagnosed multiple myeloma, a 4-fold increased incidence of second primary malignancies has been observed in patients receiving Revlimid® (7.0%) compared with controls (1.8%). Among invasive SPMs, cases of AML, MDS and solid tumours were observed in patients receiving Revlimid® in combination with melphalan or immediately following high dose melphalan and ASCT; cases of B-cell malignancies (including Hodgkin's lymphoma) were observed in the clinical trials where patients received Revlimid in the post ASCT setting.

The risk of occurrence of SPM must be taken into account before initiating treatment with Revlimid. Physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of second primary malignancies and institute treatment as indicated.

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. Lenalidomide is not an enzyme inducer. In an *in vitro* study with human hepatocytes, lenalidomide, at various concentrations tested did not induce CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP3A4/5. Therefore, induction leading to reduced efficacy of drugs, including hormonal contraceptives, is not expected if lenalidomide is administered alone. However, 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 Fertility, 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).

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.

Lenalidomide is present in human semen at extremely low levels during treatment and is undetectable in human semen 3 days after stopping the drug in the healthy subject (see section 5.2). As a precaution, and taking into account special populations with prolonged elimination time such as renal impairment, all male patients taking lenalidomide should use condoms throughout treatment duration, during dose interruption and for 1 week after cessation of treatment if their partner is pregnant or 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

a. Summary of the safety profile in patients with multiple myeloma

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 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000 including isolated reports), unknown (cannot be estimated from the available data).

b. Tabulated summary of adverse reactions

The following table is derived from data gathered during the pivotal studies. The data were not adjusted according to the greater duration of treatment in the lenalidomide/dexamethasone versus the placebo/dexamethasone arms in the pivotal studies (See section 5.1).

Table 1: ADRs reported in clinical studies in patients with multiple myeloma treated with lenalidomide

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
Infections and Infestations	**Very Common** Pneumonia, Upper respiratory tract infection **Common** Sepsis, Bacterial, viral and fungal infections (including opportunistic infections), Sinusitis	**Common** Pneumonia, Bacterial, viral and fungal infections (including opportunistic infections)
Neoplasms benign, malignant and unspecified	**Uncommon** Basal cell carcinoma Squamous skin cancer^	
Blood and Lymphatic System Disorders	**Very Common** Thrombocytopenia^, Neutropenias^, Anaemia, Haemorrhagic disorder^, Leucopenias **Common** Pancytopenia **Uncommon** Haemolysis, Autoimmune haemolytic anaemia, Haemolytic anaemia	**Very Common** Thrombocytopenia^, Neutropenias^, Leucopenias **Common** Febrile Neutropenia, Anaemia **Uncommon** Hypercoagulation, Coagulopathy
Immune System Disorders	**Uncommon** Hypersensitivity^	
Endocrine Disorders	**Common** Hypothyroidism	

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
Metabolism and Nutrition Disorders	**Very Common** Hypokalaemia, Decreased appetite **Common** Hypomagnesaemia, Hypocalcaemia, Dehydration	**Common** Hypokalaemia, Hypocalcaemia, Hypophosphataemia
Psychiatric Disorder	**Uncommon** Loss of libido	**Common** Depression
Nervous System disorders	**Very Common** Peripheral neuropathies (excluding motor neuropathy), Dizziness, Tremor, Dysgeusia, Headache **Common** Ataxia, Balance impaired	**Common** Cerebrovascular Accident, Dizziness, Syncope **Uncommon** Intracranial haemorrhage^, Transient ischaemic attack, Cerebral ischaemia
Eye Disorders	**Very Common** Blurred vision **Common** Reduced visual acuity, Cataract	**Common** Cataract **Uncommon** Blindness
Ear and Labyrinth Disorders	**Common** Deafness (Including Hypoacusis), Tinnitus	
Cardiac Disorders	**Common** Atrial Fibrillation, Bradycardia **Uncommon** Arrhythmia, QT prolongation, Atrial flutter, Ventricular extrasystoles	**Common** Myocardial infarction^, Atrial Fibrillation, Congestive Cardiac, Failure, Tachycardia
Vascular Disorders	**Very Common** Venous Thromboembolic Events, predominantly Deep Vein Thrombosis and Pulmonary Embolism^ **Common** Hypotension, Hypertension, Ecchymosis^	**Very Common** Venous Thromboembolic Events, predominantly Deep Vein Thrombosis and Pulmonary Embolism^ **Uncommon** Ischemia, Peripheral ischemia, Intracranial venous sinus thrombosis
Respiratory, Thoracic and Mediastinal Disorders	**Very common** Dyspnoea, Nasopharyngitis, Pharyngitis, Bronchitis, Epistaxis^	**Common** Respiratory Distress
Gastrointestinal Disorders	**Very Common** Constipation, Diarrhoea, Nausea, Vomiting **Common** Gastrointestinal Haemorrhage (including rectal haemorrhage, haemorrhoidal haemorrhage, peptic ulcer haemorrhage and gingival bleeding)^, Abdominal Pain, Dry Mouth, Stomatitis, Dysphagia **Uncommon** Colitis, Caecitis	**Common** Diarrhoea, Constipation, Nausea
Hepatobiliary Disorders	**Common** Abnormal Liver Function Tests	**Common** Abnormal Liver Function Tests

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
Skin and Subcutaneous tissue Disorders	**Very Common** Rashes **Common** Urticaria, Hyperhidrosis, Dry Skin, Pruritus, Skin Hyperpigmentation, Eczema **Uncommon** Skin discolouration, Photosensitivity reaction	**Common** Rashes
Musculoskeletal and connective tissue disorders	**Very Common** Muscle Spasms, Bone Pain, Musculoskeletal and connective tissue pain and discomfort **Common** Joint swelling	**Common** Muscle Weakness, Bone Pain **Uncommon** Joint swelling
Renal and Urinary Disorders	**Common** Haematuria^, Urinary retention , Urinary incontinence **Uncommon** Acquired Fanconi syndrome	**Common** Renal failure **Uncommon** Renal tubular necrosis
Reproductive System and Breast Disorders	**Common** Erectile Dysfunction	
General disorders and administration site conditions	**Very Common** Fatigue, Oedema (including peripheral oedema), Pyrexia, Influenza like illness syndrome (including pyrexia, myalgia, musculoskeletal pain, headache and rigors) **Common** Chest Pain, Lethargy	**Common** Fatigue
Injury, poisoning and procedural complications	**Common** Contusion^	

^See section 4.8c.

In addition to the above adverse drug reactions identified from the pivotal trials, the following table is derived from data gathered during post-marketing experience.

Table 2: Summary of adverse drug reactions identified from post-marketing data in patients treated with lenalidomide

System organ class	Reactions/frequency
Neoplasms benign, malignant and unspecified	Rare: Tumour lysis syndrome
Respiratory, Thoracic and Mediastinal Disorders	Unknown: Interstitial pneumonitis
Gastrointestinal disorders	Unknown: Pancreatitis
Skin and subcutaneous system disorders	Uncommon: Angioedema Rare: Stevens-Johnson Syndrome^, toxic epidermal necrolysis^

^see section 4.8c

c. Description of selected adverse reactions

Teratogenicity
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.

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). Grade 4 febrile neutropenia episodes were observed infrequently (0.6% in lenalidomide/dexamethasone-treated patients compared to 0.0% in placebo/dexamethasone treated patients).

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).

Venous thromboembolism
The combination of lenalidomide with dexamethasone is associated with an increased risk of DVT and PE in patients with multiple myeloma (see section 4.5). Concomitant administration of erythropoietic agents or previous history of DVT may also increase thrombotic risk in these patients.

Myocardial Infarction
Myocardial infarction has been reported in patients receiving lenalidomide, particularly in those with known risk factors.

Haemorrhagic disorders
Haemorrhagic disorders are listed under several system organ classes: Blood and lymphatic system disorders; nervous system disorders (intracranial haemorrhage); respiratory, thoracic and mediastinal disorders (epistaxis); gastrointestinal disorders (gingival bleeding, haemorrhoidal haemorrhage, rectal haemorrhage); renal and urinary disorders (haematuria); Injury, poisoning and procedural complications (contusion) and vascular disorders (ecchymosis).

Allergic Reactions
Cases of allergic reaction/hypersensitivity reactions have been reported. A possible cross-reaction between lenalidomide and thalidomide has been reported in the literature.

Severe skin reactions
Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported. Patients with a history of severe rash associated with thalidomide treatment should not receive lenalidomide.

Second Primary Malignancies
*In clinical trials in previously treated myeloma patients with Lenalidomide/Dexamethasone compared to controls, mainly comprising of basal cell or squamous cell skin cancers.

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 150 mg, and in single-dose studies, some patients were exposed to up to 400 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 (median follow-up duration of 98.0 weeks). Complete response and overall response 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.

An extended follow-up efficacy analysis was conducted with a median follow-up of 130.7 weeks. Table 1 summarises the results of the follow-up efficacy analyses – pooled studies MM-009 and MM-010.

In this pooled extended follow-up analysis, the median TTP was 60.1 weeks (95% CI: 44.3, 73.1) in patients treated with lenalidomide/dexamethasone (N = 353) versus 20.1 weeks (95% CI: 17.7, 20.3) in patients treated with placebo/dexamethasone (N = 351). The median progression free survival was 48.1 weeks (95% CI: 36.4, 62.1) in patients treated with lenalidomide/dexamethasone versus 20.0 weeks (95% CI: 16.1, 20.1) in patients treated with placebo/dexamethasone. The median duration of treatment was 44.0 weeks (min: 0.1, max: 254.9) for lenalidomide/dexamethasone and 23.1 weeks (min: 0.3, max: 238.1) for placebo/dexamethasone). Complete response (CR), partial response (PR) and overall response (CR+PR) rates in the lenalidomide/dexamethasone arm remain significantly

higher than in the dexamethasone/placebo arm in both studies. The median overall survival in the extended follow-up analysis of the pooled studies is 164.3 weeks (95% CI: 145.1, 192.6) in patients treated with lenalidomide/dexamethasone versus 136.4 weeks (95% CI: 113.1, 161.7) in patients treated with placebo/dexamethasone. Despite the fact that 170 out of the 351 patients randomised to placebo/dexamethasone received lenalidomide after disease progression or after the studies were unblinded, the pooled analysis of overall survival demonstrated a statistically significant survival advantage for lenalidomide/dexamethasone relative to placebo/dexamethasone (hazard ratio = 0.833, 95% CI = [0.687, 1.009], p=0.045).

Table 1: Summary of Results of Efficacy Analyses as of cut-off date for extended follow-up — Pooled Studies MM-009 and MM-010 (cut-offs 23 July 2008 and 2 March 2008, respectively)

Endpoint	**len/dex (N=353)**	**placebo/dex (N=351)**	
Time to Event			**Hazard ratio [95% CI], p-value** [a]
Time To Progression Median [95% CI], weeks	60.1 [44.3, 73.1]	20.1 [17.7, 20.3]	0.350 [0.287, 0.426], p < 0.001
Progression Free Survival Median [95% CI], weeks	48.1 [36. 4, 62.1]	20.0 [16.1, 20.1]	0.393 [0.326, 0.473] p < 0.001 [b]
Overall Survival Median [95% CI], weeks 1-year Overall Survival rate	164.3 [145.1, 192.6] 82%	136.4 [113.1, 161.7] 75%	0.833 [0. 687, 1.009] p = 0.045
Response rate			**Odds ratio [95% CI], p-value** [b]
Overall Response [n, %] Complete Response [n, %]	212 (60.1) 58 (16.4)	75 (21.4) 11 (3.1)	5.53 [3.97, 7.71], p < 0.001 6.08 [3.13, 11.80], p < 0.001

a: Two-tailed log rank test comparing survival curves between treatment groups.
b: Two-tailed continuity-corrected chi-square test.

Exploratory study

An open-label, randomized, multicenter, Phase 3 study was conducted in 445 patients with newly diagnosed multiple myeloma; 222 patients were randomized to the lenalidomide/low dose dexamethasone arm, and 223 were randomized to the lenalidomide/standard dose dexamethasone arm. Patients randomized to the lenalidomide/standard dose dexamethasone arm received lenalidomide 25 mg/day, Days 1 to 21 every 28 days plus dexamethasone 40 mg/day on Days 1 to 4, 9 to 12, and 17 to 20 every 28 days for the first four cycles. Patients randomized to the lenalidomide/low dose dexamethasone arm received lenalidomide 25 mg/day, Days 1 to 21 every 28 days plus low dose dexamethasone – 40 mg/day on Days 1, 8, 15, and 22 every 28 days. In the lenalidomide/low dose dexamethasone group, 20 patients (9.1%) underwent at least one dose interruption compared to 65 patients (29.3%) in the lenalidomide/standard dose dexamethasone arm.

In a post-hoc analysis, lower mortality was observed in the lenalidomide/low dose dexamethasone arm 6.8% (15/220) compared to the lenalidomide/standard dose dexamethasone arm 19.3% (43/223), in the newly diagnosed multiple myeloma patient population, with a median follow up of 72.3 weeks.

However with a longer follow-up, the difference in overall survival in favour of low dose dexamethasone tends to decrease.

Considering that the patient population differs from the authorised indication, these results should be interpreted with caution.

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 is rapidly absorbed following oral administration in healthy volunteers, under fasting conditions, with maximum plasma concentrations occurring between 0.5 and 2 hours post-dose. In patients, as well as in healthy volunteers, the maximum concentration (C_{max}) and area-under-the-concentration time curve (AUC) increase proportionally 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.

Co-administration with a high-fat and high-calorie meal in healthy volunteers reduces the extent of absorption, resulting in an approximately 20% decrease in area under the concentration versus time curve (AUC) and 50% decrease in Cmax in plasma. However, in the pivotal multiple myeloma registration trials where the efficacy and safety were established for lenalidomide, the drug was administered without regard to food intake. Thus, lenalidomide can be administered with or without food.

Distribution
In vitro (^{14}C)-lenalidomide binding to plasma proteins was low with mean plasma protein binding at 23% and 29% in multiple myeloma patients and healthy volunteers, respectively.

Lenalidomide is present in human semen (< 0.01% of the dose) after administration of 25 mg/day and the drug is undetectable in semen of a healthy subject 3 days after stopping the drug (see section 4.4).

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 through urinary excretion. The contribution of renal excretion to total clearance in subjects with normal renal function was 90%, with 4% of lenalidomide eliminated in faeces.

Lenalidomide is poorly metabolized as 82% of the dose is excreted unchanged in urine. Hydroxy-lenalidomide and N-acetyl-lenalidomide represent 4.59% and 1.83% of the excreted dose, respectively. The renal clearance of lenalidomide exceeds the glomerular filtration rate and therefore is at least actively secreted to some extent.
At recommended doses (5 to 25 mg/day), half-life in plasma is approximately 3 hours in healthy volunteers and patients with multiple myeloma.

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.

5.3 Preclinical safety data

An embryofoetal development study has been conducted in monkeys administered lenalidomide at doses from 0.5 and up to 4 mg/kg/day. Findings from this study indicate that lenalidomide produced external malformations including non-patent anus and malformations of upper and lower extremities

(bent, shortened, malformed, malrotated and/or absent part of the extremities, oligo and/or polydactyly) in the offspring of female monkeys who received the drug during pregnancy. Various visceral effects (discoloration, red foci at different organs, small colorless mass above atrio-ventricular valve, small gall bladder, malformed diaphragm) were also observed in single fetuses.

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 comparisons.

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

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
1 Longwalk Road
Stockley Park
Uxbridge
UB11 1DB
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 website of the European Medicines Agency: http://www.ema.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 opened, 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). Prescribing physicians should carefully evaluate which dose of dexamethasone to use, taking into account the condition and disease status of the patient.

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 1, 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.

No dose adjustments are required for patients with mild renal impairment. The following dose adjustments are recommended at the start of therapy for patients with moderate or severe impaired renal function or end stage renal disease.

Renal Function (CLcr)	Dose Adjustment
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)	5 mg once daily. On dialysis days, the dose should be administered following 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.

** The dose may be escalated to 10 mg once daily if the patient is tolerating the treatment

After initiation of lenalidomide therapy, subsequent lenalidomide dose modification in renally impaired patients should be based on individual patient treatment tolerance, as described above.

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.

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
- 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, pharmacokinetic data has demonstrated that lenalidomide is present in human semen at extremely low levels during treatment and is undetectable in human semen 3 days after stopping the drug in the healthy subject (see section 5.2). As a precaution, all male patients taking lenalidomide must meet the following conditions:
- Understand the expected teratogenic risk if engaged in sexual activity with a pregnant woman or a woman of childbearing potential
- Understand the need for the use of a condom if engaged in sexual activity with a pregnant woman or a woman of childbearing potential.

The prescriber must ensure that for women of childbearing potential:
- The patient complies with the conditions of the 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
Lenalidomide is present in human semen at extremely low levels during treatment and is undetectable in human semen 3 days after stopping the drug in the healthy subject (see section 5.2). As a precaution, and taking into account special populations with prolonged elimination time such as renal impairment, all male patients taking lenalidomide should use condoms throughout treatment duration, during dose interruption and for 1 week after cessation of treatment if their partner is pregnant or 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 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.

Other special warnings and precautions for use

Cardiovascular disorders

Myocardial Infarction
Myocardial infarction has been reported in patients receiving lenalidomide, particularly in those with known risk factors. Patients with known risk factors – including prior thrombosis – should be closely monitored, and action should be taken to try to minimize all modifiable risk factors (eg. smoking, hypertension, and hyperlipidaemia).

Venous and arterial thromboembolic events
In patients with multiple myeloma, the combination of lenalidomide with dexamethasone is associated with an increased risk of venous thromboembolism (predominantly deep vein thrombosis and pulmonary embolism) and arterial thromboembolism (predominantly myocardial infarction and cerebrovascular event) – see sections 4.5 and 4.8.

Consequently, patients with known risk factors for thromboembolism – including prior thrombosis – should be closely monitored. Action should be taken to try to minimize all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia). Concomitant administration of erythropoietic agents or previous history of thromboembolic events 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 12 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 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.

If the patient experiences any thromboembolic events, treatment must be discontinued and standard anticoagulation therapy started. Once the patient has been stabilised on the anticoagulation treatment and any complications of the thromboembolic event have been managed, the lenalidomide treatment may be restarted at the original dose dependent upon a benefit risk assessment. The patient should continue anticoagulation therapy during the course of lenalidomide treatment.

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, especially in case of concomitant medication susceptible to induce bleeding (see Section 4.8 Haemorrhagic disorders). A dose reduction of lenalidomide 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.

Allergic Reactions
Cases of allergic reaction/hypersensitivity reactions have been reported (see section 4.8). Patients who had previous allergic reactions while treated with thalidomide should be monitored closely, as a possible cross-reaction between lenalidomide and thalidomide has been reported in the literature.

Severe skin reactions
Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported. Lenalidomide must be discontinued for exfoliative or bullous rash, or if SJS or TEN is suspected, and should not be resumed following discontinuation for these reactions. Interruption or discontinuation of lenalidomide should be considered for other forms of skin reaction depending on severity. Patients with a history of severe rash associated with thalidomide treatment should not receive lenalidomide.

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.

Second Primary Malignancies

An increase of second primary malignancies (SPM) has been observed in clinical trials in previously treated myeloma patients receiving lenalidomide/dexamethasone (3.98 per 100 patient-years) compared to controls (1.38 per 100 patient-years). Non invasive SPM comprise basal cell or squamous cell skin cancers. Most of the invasive SPMs were solid tumour malignancies.

In clinical trials of newly diagnosed multiple myeloma, a 4-fold increased incidence of second primary malignancies has been observed in patients receiving Revlimid (7.0%) compared with controls (1.8%). Among invasive SPMs, cases of AML, MDS and solid tumours were observed in patients receiving Revlimid in combination with melphalan or immediately following high dose melphalan and ASCT; cases of B-cell malignancies (including Hodgkin's lymphoma) were observed in the clinical trials where patients received Revlimid in the post ASCT setting.

The risk of occurrence of SPM must be taken into account before initiating treatment with Revlimid. Physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of second primary malignancies and institute treatment as indicated.

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. Lenalidomide is not an enzyme inducer. In an *in vitro* study with human hepatocytes, lenalidomide, at various concentrations tested did not induce CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP3A4/5. Therefore, induction leading to reduced efficacy of drugs, including hormonal contraceptives, is not expected if lenalidomide is administered alone. However, 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 Fertility, 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).

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.

Lenalidomide is present in human semen at extremely low levels during treatment and is undetectable in human semen 3 days after stopping the drug in the healthy subject (see section 5.2). As a precaution, and taking into account special populations with prolonged elimination time such as renal impairment, all male patients taking lenalidomide should use condoms throughout treatment duration, during dose interruption and for 1 week after cessation of treatment if their partner is pregnant or 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

a. Summary of the safety profile in patients with multiple myeloma

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 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000 including isolated reports), unknown (cannot be estimated from the available data).

b. Tabulated summary of adverse reactions

The following table is derived from data gathered during the pivotal studies. The data were not adjusted according to the greater duration of treatment in the lenalidomide/dexamethasone versus the placebo/dexamethasone arms in the pivotal studies (See section 5.1).

Table 1: ADRs reported in clinical studies in patients with multiple myeloma treated with lenalidomide

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
Infections and Infestations	**Very Common** Pneumonia, Upper respiratory tract infection **Common** Sepsis, Bacterial, viral and fungal infections (including opportunistic infections), Sinusitis	**Common** Pneumonia, Bacterial, viral and fungal infections (including opportunistic infections)

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
Neoplasms benign, malignant and unspecified	**Uncommon** Basal cell carcinoma Squamous skin cancer^	
Blood and Lymphatic System Disorders	**Very Common** Thrombocytopenia^, Neutropenias^, Anaemia, Haemorrhagic disorder^, Leucopenias **Common** Pancytopenia **Uncommon** Haemolysis, Autoimmune haemolytic anaemia, Haemolytic anaemia	**Very Common** Thrombocytopenia^, Neutropenias^, Leucopenias **Common** Febrile Neutropenia, Anaemia **Uncommon** Hypercoagulation, Coagulopathy
Immune System Disorders	**Uncommon** Hypersensitivity^	
Endocrine Disorders	**Common** Hypothyroidism	
Metabolism and Nutrition Disorders	**Very Common** Hypokalaemia, Decreased appetite **Common** Hypomagnesaemia, Hypocalcaemia, Dehydration	**Common** Hypokalaemia, Hypocalcaemia, Hypophosphataemia
Psychiatric Disorder	**Uncommon** Loss of libido	**Common** Depression
Nervous System disorders	**Very Common** Peripheral neuropathies (excluding motor neuropathy), Dizziness, Tremor, Dysgeusia, Headache **Common** Ataxia, Balance impaired	**Common** Cerebrovascular Accident, Dizziness, Syncope **Uncommon** Intracranial haemorrhage^, Transient ischaemic attack, Cerebral ischaemia
Eye Disorders	**Very Common** Blurred vision **Common** Reduced visual acuity, Cataract	**Common** Cataract **Uncommon** Blindness
Ear and Labyrinth Disorders	**Common** Deafness (Including Hypoacusis), Tinnitus	
Cardiac Disorders	**Common** Atrial Fibrillation, Bradycardia **Uncommon** Arrhythmia, QT prolongation, Atrial flutter, Ventricular extrasystoles	**Common** Myocardial infarction^, Atrial Fibrillation, Congestive Cardiac, Failure, Tachycardia
Vascular Disorders	**Very Common** Venous Thromboembolic Events, predominantly Deep Vein Thrombosis and Pulmonary Embolism^ **Common** Hypotension, Hypertension, Ecchymosis^	**Very Common** Venous Thromboembolic Events, predominantly Deep Vein Thrombosis and Pulmonary Embolism^ **Uncommon** Ischemia, Peripheral ischemia, Intracranial venous sinus thrombosis

System Organ Class / Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
Respiratory, Thoracic and Mediastinal Disorders	**Very common** Dyspnoea, Nasopharyngitis, Pharyngitis, Bronchitis, Epistaxis^	**Common** Respiratory Distress
Gastrointestinal Disorders	**Very Common** Constipation, Diarrhoea, Nausea, Vomiting **Common** Gastrointestinal Haemorrhage (including rectal haemorrhage, haemorrhoidal haemorrhage, peptic ulcer haemorrhage and gingival bleeding)^, Abdominal Pain, Dry Mouth, Stomatitis, Dysphagia **Uncommon** Colitis, Caecitis	**Common** Diarrhoea, Constipation, Nausea
Hepatobiliary Disorders	**Common** Abnormal Liver Function Tests	**Common** Abnormal Liver Function Tests
Skin and Subcutaneous tissue Disorders	**Very Common** Rashes **Common** Urticaria, Hyperhidrosis, Dry Skin, Pruritus, Skin Hyperpigmentation, Eczema **Uncommon** Skin discolouration, Photosensitivity reaction	**Common** Rashes
Musculoskeletal and connective tissue disorders	**Very Common** Muscle Spasms, Bone Pain, Musculoskeletal and connective tissue pain and discomfort **Common** Joint swelling	**Common** Muscle Weakness, Bone Pain **Uncommon** Joint swelling
Renal and Urinary Disorders	**Common** Haematuria^, Urinary retention , Urinary incontinence **Uncommon** Acquired Fanconi syndrome	**Common** Renal failure **Uncommon** Renal tubular necrosis
Reproductive System and Breast Disorders	**Common** Erectile Dysfunction	
General disorders and administration site conditions	**Very Common** Fatigue, Oedema (including peripheral oedema), Pyrexia, Influenza like illness syndrome (including pyrexia, myalgia, musculoskeletal pain, headache and rigors) **Common** Chest Pain, Lethargy	**Common** Fatigue
Injury, poisoning and procedural complications	**Common** Contusion^	

^See section 4.8c.

In addition to the above adverse drug reactions identified from the pivotal trials, the following table is derived from data gathered during post-marketing experience.

Table 2: Summary of adverse drug reactions identified from post-marketing data in patients treated with lenalidomide

System organ class	Reactions/frequency
Neoplasms benign, malignant and unspecified	Rare: Tumour lysis syndrome
Respiratory, Thoracic and Mediastinal Disorders	Unknown: Interstitial pneumonitis
Gastrointestinal disorders	Unknown: Pancreatitis
Skin and subcutaneous system disorders	Uncommon: Angioedema Rare: Stevens-Johnson Syndrome^, toxic epidermal necrolysis^

^see section 4.8c

c. Description of selected adverse reactions

Teratogenicity
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.

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). Grade 4 febrile neutropenia episodes were observed infrequently (0.6% in lenalidomide/dexamethasone-treated patients compared to 0.0% in placebo/dexamethasone treated patients).

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).

Venous thromboembolism
The combination of lenalidomide with dexamethasone is associated with an increased risk of DVT and PE in patients with multiple myeloma (see section 4.5). Concomitant administration of erythropoietic agents or previous history of DVT may also increase thrombotic risk in these patients.

Myocardial Infarction
Myocardial infarction has been reported in patients receiving lenalidomide, particularly in those with known risk factors.

Haemorrhagic disorders
Haemorrhagic disorders are listed under several system organ classes: Blood and lymphatic system disorders; nervous system disorders (intracranial haemorrhage); respiratory, thoracic and mediastinal disorders (epistaxis); gastrointestinal disorders (gingival bleeding, haemorrhoidal haemorrhage, rectal haemorrhage); renal and urinary disorders (haematuria); Injury, poisoning and procedural complications (contusion) and vascular disorders (ecchymosis).

Allergic Reactions
Cases of allergic reaction/hypersensitivity reactions have been reported. A possible cross-reaction between lenalidomide and thalidomide has been reported in the literature.

Severe skin reactions
Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported. Patients with a history of severe rash associated with thalidomide treatment should not receive lenalidomide.

Second Primary Malignancies
*In clinical trials in previously treated myeloma patients with Lenalidomide/Dexamethasone compared to controls, mainly comprising of basal cell or squamous cell skin cancers.

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 150 mg, and in single-dose studies, some patients were exposed to up to 400 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 (median follow-up duration of 98.0 weeks). Complete response and overall response 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.

An extended follow-up efficacy analysis was conducted with a median follow-up of 130.7 weeks. Table 1 summarises the results of the follow-up efficacy analyses – pooled studies MM-009 and MM-010.

In this pooled extended follow-up analysis, the median TTP was 60.1 weeks (95% CI: 44.3, 73.1) in patients treated with lenalidomide/dexamethasone (N = 353) versus 20.1 weeks (95% CI: 17.7, 20.3) in patients treated with placebo/dexamethasone (N = 351). The median progression free survival was 48.1 weeks (95% CI: 36.4, 62.1) in patients treated with lenalidomide/dexamethasone versus 20.0 weeks (95% CI: 16.1, 20.1) in patients treated with placebo/dexamethasone. The median duration of treatment was 44.0 weeks (min: 0.1, max: 254.9) for lenalidomide/dexamethasone and 23.1 weeks (min: 0.3, max: 238.1) for placebo/dexamethasone). Complete response (CR), partial response (PR) and overall response (CR+PR) rates in the lenalidomide/dexamethasone arm remain significantly higher than in the dexamethasone/placebo arm in both studies. The median overall survival in the extended follow-up analysis of the pooled studies is 164.3 weeks (95% CI: 145.1, 192.6) in patients treated with lenalidomide/dexamethasone versus 136.4 weeks (95% CI: 113.1, 161.7) in patients treated with placebo/dexamethasone. Despite the fact that 170 out of the 351 patients randomised to placebo/dexamethasone received lenalidomide after disease progression or after the studies were unblinded, the pooled analysis of overall survival demonstrated a statistically significant survival advantage for lenalidomide/dexamethasone relative to placebo/dexamethasone (hazard ratio = 0.833, 95% CI = [0.687, 1.009], p=0.045).

Table 1: Summary of Results of Efficacy Analyses as of cut-off date for extended follow-up — Pooled Studies MM-009 and MM-010 (cut-offs 23 July 2008 and 2 March 2008, respectively)

Endpoint	**len/dex (N=353)**	**placebo/dex (N=351)**	
Time to Event			**Hazard ratio [95% CI], p-value** [a]
Time To Progression Median [95% CI], weeks	60.1 [44.3, 73.1]	20.1 [17.7, 20.3]	0.350 [0.287, 0.426], p < 0.001 [c]
Progression Free Survival Median [95% CI], weeks	48.1 [36. 4, 62.1]	20.0 [16.1, 20.1]	0.393 [0.326, 0.473] p < 0.001
Overall Survival Median [95% CI], weeks 1-year Overall Survival rate	164.3 [145.1, 192.6] 82%	136.4 [113.1, 161.7] 75%	0.833 [0. 687, 1.009] p = 0.045
Response rate			**Odds ratio [95% CI], p-value** [b]
Overall Response [n, %] Complete Response [n, %]	212 (60.1) 58 (16.4)	75 (21.4) 11 (3.1)	5.53 [3.97, 7.71], p < 0.001 6.08 [3.13, 11.80], p < 0.001

a: Two-tailed log rank test comparing survival curves between treatment groups.
b: Two-tailed continuity-corrected chi-square test.

Exploratory study

An open-label, randomized, multicenter, Phase 3 study was conducted in 445 patients with newly diagnosed multiple myeloma; 222 patients were randomized to the lenalidomide/low dose dexamethasone arm, and 223 were randomized to the lenalidomide/standard dose dexamethasone arm.

Patients randomized to the lenalidomide/standard dose dexamethasone arm received lenalidomide 25 mg/day, Days 1 to 21 every 28 days plus dexamethasone 40 mg/day on Days 1 to 4, 9 to 12, and 17 to 20 every 28 days for the first four cycles. Patients randomized to the lenalidomide/low dose dexamethasone arm received lenalidomide 25 mg/day, Days 1 to 21 every 28 days plus low dose dexamethasone – 40 mg/day on Days 1, 8, 15, and 22 every 28 days. In the lenalidomide/low dose dexamethasone group, 20 patients (9.1%) underwent at least one dose interruption compared to 65 patients (29.3%) in the lenalidomide/standard dose dexamethasone arm.

In a post-hoc analysis, lower mortality was observed in the lenalidomide/low dose dexamethasone arm 6.8% (15/220) compared to the lenalidomide/standard dose dexamethasone arm 19.3% (43/223), in the newly diagnosed multiple myeloma patient population, with a median follow up of 72.3 weeks.

However with a longer follow-up, the difference in overall survival in favour of low dose dexamethasone tends to decrease.

Considering that the patient population differs from the authorised indication, these results should be interpreted with caution.

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 is rapidly absorbed following oral administration in healthy volunteers, under fasting conditions, with maximum plasma concentrations occurring between 0.5 and 2 hours post-dose. In patients, as well as in healthy volunteers, the maximum concentration (C_{max}) and area-under-the-concentration time curve (AUC) increase proportionally 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.

Co-administration with a high-fat and high-calorie meal in healthy volunteers reduces the extent of absorption, resulting in an approximately 20% decrease in area under the concentration versus time curve (AUC) and 50% decrease in Cmax in plasma. However, in the pivotal multiple myeloma registration trials where the efficacy and safety were established for lenalidomide, the drug was administered without regard to food intake. Thus, lenalidomide can be administered with or without food.

Distribution
In vitro (^{14}C)-lenalidomide binding to plasma proteins was low with mean plasma protein binding at 23% and 29% in multiple myeloma patients and healthy volunteers, respectively.

Lenalidomide is present in human semen (< 0.01% of the dose) after administration of 25 mg/day and the drug is undetectable in semen of a healthy subject 3 days after stopping the drug (see section 4.4).

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 through urinary excretion. The contribution of renal excretion to total clearance in subjects with normal renal function was 90%, with 4% of lenalidomide eliminated in faeces.

Lenalidomide is poorly metabolized as 82% of the dose is excreted unchanged in urine. Hydroxy-lenalidomide and N-acetyl-lenalidomide represent 4.59% and 1.83% of the excreted dose,

respectively. The renal clearance of lenalidomide exceeds the glomerular filtration rate and therefore is at least actively secreted to some extent.
At recommended doses (5 to 25 mg/day), half-life in plasma is approximately 3 hours in healthy volunteers and patients with multiple myeloma.

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.

5.3 Preclinical safety data

An embryofoetal development study has been conducted in monkeys administered lenalidomide at doses from 0.5 and up to 4 mg/kg/day. Findings from this study indicate that lenalidomide produced external malformations including non-patent anus and malformations of upper and lower extremities (bent, shortened, malformed, malrotated and/or absent part of the extremities, oligo and/or polydactyly) in the offspring of female monkeys who received the drug during pregnancy.

Various visceral effects (discoloration, red foci at different organs, small colorless mass above atrio-ventricular valve, small gall bladder, malformed diaphragm) were also observed in single fetuses.

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 comparisons.

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

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
1 Longwalk Road
Stockley Park
Uxbridge
UB11 1DB
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 website of the European Medicines Agency: http://www.ema.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

Celgene Europe Limited
1 Longwalk Road
Stockley Park
Uxbridge
UB11 1DB
United Kingdom

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

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 (SmPC) 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 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 and post-marketing experience
    - 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 pregnant or 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

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 pregnant or a WCBP (even if man has had vasectomy)
    - During Revlimid treatment
    - For one week following final dose

- 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, presented in module 1.8.1 of the Marketing Authorisation, is in place and functioning before and whilst the product is placed on the market.

Risk Management Plan
The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan as agreed in version 16.0 of the Risk Management Plan (RMP) presented in module 1.8.2 of the Marketing Authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, any updated RMP should be submitted at the same time as the following 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 European Medicines Agency

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.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

This medicinal product does not require any special storage conditions.

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
1 Longwalk Road
Stockley Park
Uxbridge
UB11 1DB
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 Limited

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.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

This medicinal product does not require any special storage conditions.

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
1 Longwalk Road
Stockley Park
Uxbridge
UB11 1DB
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 Limited

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.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

This medicinal product does not require any special storage conditions.

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
1 Longwalk Road
Stockley Park
Uxbridge
UB11 1DB
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 Limited

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.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

This medicinal product does not require any special storage conditions.

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
1 Longwalk Road
Stockley Park
Uxbridge
UB11 1DB
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 Limited

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.

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
Revlimid passes into human semen. If your female partner is pregnant or 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.

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

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").

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 Revlimid, 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.

Your doctor may reduce your dose of dexamethasone based on your general condition (see Section 2, "Take special care with Revlimid”).

How and when to take Revlimid
You should swallow the Revlimid capsules whole, preferably with water, once a day. Do not break, open 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	Affects more than 1 user in 10
Common	Affects 1 to 10 users in 100
Uncommon	Affects 1 to 10 users in 1,000
Rare	Affects 1 to 10 users in 10,000
Not known	Cannot be estimated from the available data

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

It is important to note that a small number of patients with multiple myeloma may develop additional types of cancer, and it is possible that this risk may be increased with Revlimid treatment, therefore your doctor should carefully evaluate the benefit and risk when you are prescribed Revlimid.

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, which may lead to bleeding disorders) and red blood cells (anaemia leading to tiredness and weakness)
- Constipation, diarrhoea, nausea, rashes, vomiting, muscle cramps, muscle aches, bone pain, tiredness, generalised swelling including swelling of the limbs
- Fever and flu like symptoms including fever, muscle ache, headache, and chills
- Numbness, tingling or burning sensation to the skin, pains in hands or feet, dizziness, tremor, taste disturbance
- Decreased appetite, low levels of potassium in the blood
- Leg pain (which could be a symptom of thrombosis), chest pain or shortness of breath (which may be a symptom of blood clots in the lungs)
- Infection of the lung and the upper respiratory tract, shortness of breath, nosebleed

- Blurred vision
- Headache

Common side effects are given below. You should consult your doctor if you experience any of these:
- Chest pain
- Difficulty breathing
- Infections of all types
- Infection of the sinuses that surround the nose
- Bleeding from the gums, stomach, or bowels, bruising
- Increased blood pressure or a fall in blood pressure, slow, fast or irregular heart beat
- Increased pigmentation of skin
- Skin eruptions, skin cracking, flaking
- Hives, itching, dry skin, increased sweating, dehydration
- Sore inflamed mouth, dry mouth, difficulty swallowing
- Abdominal pain
- Production of much more or much less urine than usual (which may be a symptom of kidney failure), passing blood in the urine
- Shortness of breath especially when lying down (which may be a symptoms of heart failure)
- Difficulty in obtaining an erection
- Chest pain spreading to the arms, neck, jaw, back or stomach, feeling sweaty and breathless, feeling sick or vomiting (which may be symptoms of a heart attack/myocardial infarction)
- Stroke, fainting
- Muscle weakness
- Joint swelling
- Changes to blood thyroid hormone, low levels of calcium, phosphate or magnesium in the blood
- Depression
- Cataract
- Reduced vision
- Deafness
- Abnormal liver test results
- Impaired balance, movement difficulty
- Ringing in the ears (tinnitus)

Uncommon side effects are given below. You should consult your doctor if you experience any of these:
-
- Bleeding within the skull
- Circulatory problems
- Loss of vision
- Loss of libido (sex drive)
- Passing large amount of urine with bone pain and weakness, which may be symptoms of Fanconi syndrome (a kidney disorder)
- Colitis and caecitis (inflammation of the large intestine), both of which may be manifested as abdominal pain, bloating, or diarrhoea
- Renal tubular necrosis (a type of kidney impairment) which may be evident by production of much more or much less urine than usual
- Skin discoloration, sensitivity to sunlight
- Certain types of tumour of skin
- Hypersensitivity/Angioedema (types of allergic reaction that may be manifested as hives, rashes, swelling of eyes, mouth or face, difficulty of breathing, or itching)

Rare side effects are given below. You should consult your doctor if you experience any of these:
- Serious allergic reaction that may begin as rash in one area but spread with extensive loss of skin over the whole body

- Tumour lysis syndrome - metabolic complications that can occur during treatment of cancer and sometimes even without treatment. These complications are caused by the break-down products of dying cancer cells and may include the following: changes to blood chemistry; high potassium, phosphorus, uric acid, and low calcium consequently leading to changes in kidney function, heart beat, seizures, and sometimes death

Side effects where the frequency is not known are given below. You should consult your doctor if you experience any of these:
- Sudden, or mild but worsening pain in the upper abdomen and/or back, which remains for a few days, possibly accompanied by nausea, vomiting, fever and a rapid pulse − these symptoms may be due to inflammation of the pancreas.
- Wheezing, shortness of breath or a dry cough, which may be symptoms caused by inflammation of the tissue in the lungs.

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.
- This medicinal product does not require any special storage conditions.
- 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.

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

This leaflet was last approved in XX/YYYY

Detailed information on this medicine is available on the website of the European Medicines Agency: http://www.ema.europa.eu/.